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SOME RECENT STUDIES IN THE IMMUNOLOGY OF CANCER. I. DETECTION OF METHYL-CHOLANTHRENE-LIKE SUBSTANCE BY THE SCHULTZ-DALE METHOD IN THE SERA OF PATIENTS WITH TUMORS AND IN SOME APPARENTLY HEALTHY PERSONS

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The proper selection of immunizing antigens from homogenates of cancer tissue determines to a great extent the type of information one obtains from the use of the Schultz-Dale test[1] in the diagnosis of cancer. Using the sediment obtained from aqueous carcinoma emulsions centrifuged at 3,200 to 4,000 rpm, Makari (1) obtained results which were highly specific for carcinoma (96.8 per cent positive in carcinoma and only 4.8 per cent positive in noncancerous lesions). Burrows (2) confirmed these findings in a large series of cases. He obtained 96.7 per cent positive results in carcinoma, and only 3.3 per cent positive results in noncancerous lesions. Accordingly this procedure could well serve as a specific *diagnostic test for carcinoma.*

By using the sediment obtained at 3,000 to 10,000 rpm, Makari (3) presented evidence, based on a study of 566 subjects, that the method could be utilized as a *tumor-screening procedure.*

The purpose of this article is to present a further possible use of the Schultz-Dale test. It can serve as a *screening method* for *methyl-cholanthrene-like* substances in the sera, not only of patients with cancer, but also of certain supposedly healthy persons.

MATERIALS AND METHODS

The Schultz-Dale test was performed as reported by us earlier (1, 3). Carcinoma sediments obtained at 3,000 to 10,000 rpm from homogenates of carcinoma of the colon, cervix, and lung were used for the active immunization of guinea pigs. In addition, the supernatant solutions obtained at 10,000 rpm from these same homogenates were used to immunize a second group of guinea pigs. In a third group, the carcinoma homogenates were replaced by methyl-cholanthrene (M.C.) (0.2 mg. with 0.5 ml. of Freund's adjuvants per dose). Freund's adjuvants were used in all these experiments.

The 3 groups of guinea pigs were sacrificed after one month of immunization and their uterine horns (which had become coated with antibodies as a result of the immunization)

[1] In this test, a segment of smooth muscle from a guinea-pig uterus which is coated with antibodies is used as an indicator of antigen-antibody reactions.

were then placed in a Schultz-Dale bath. Normal serum was repeatedly added to these horns to neutralize antibodies against normal tissue antigens. To "release the reaction" in these neutralized horns (*i.e.*, to induce specific anaphylactic contraction of the uterine horn from an immunized pig in the presence of specific antigen), sera from 67 patients with proved tumors were added. Thus the presence of carcinoma antigens or M.C. could be determined. The results of the specific contraction of each horn were recorded in millimeters. Then a "Contraction Index" was calculated. This is the ratio of the specific contraction produced by a given antigen to that produced by 10 γ of histamine base. Results of these studies are shown in Table 1.

In such an experiment, differences among the individuals of a given group would not be especially significant because of the smallness of the group. Another study was undertaken to eliminate this factor.

In the second experiment (Table 2), 44 subjects were simultaneously tested for both carcinoma and M.C.-like antigens. One group of guinea pigs was immunized with carcinoma and the other group with M.C. The sera were tested as unknowns, divided into 2 batches, given different numbers, and sent to the examiner without informing him of this procedure. These sera were then used to release the reaction in the uterine horns from guinea pigs immunized with carcinoma, and also in the horns from guinea pigs immunized with M.C.

Carcinoma antigens and M.C.-like substances were found to a much greater extent in patients with carcinoma, less so in patients with other diseases, and much less so in healthy persons. In all 3 groups, however, there was more M.C.-like substance than carcinoma antigen. These two facts indicate a close relationship between the two antigens.

Next we wanted to check the suspected relationship between the M.C.-like constituent in the sera of the positive cases and M.C. itself. This could be established if the addition of M.C. to normal serum would produce the same reaction when that serum was substituted for the sera of our carcinoma patients, and tested in the Schultz-Dale bath with the immunized uterine horns of our sensitized guinea pigs. These tests were carried out and it was found that M.C. added to normal serum would "release the reaction," *i.e.*, induce an anaphylactic contraction of the uterine horn even after complete desensitization to the normal serum alone (Tables 3 and 4).

In the latter experiments, both M.C. in Tyrode's solution and M.C. in normal serum were used to release the reaction. To insure a good degree of dispersion and homogenization, both M.C. in Tyrode and M.C. in normal serum were sonically treated for ten minutes. Normal serum was used with M.C. in this experiment as a "schlepper" (a protein added to an "incomplete" antigen or a "hapten" to increase antigenicity).

It soon became apparent that M.C. is not a "complete" antigen, but that it behaves as a "hapten" in requiring the presence of normal serum to release the reactions in a Schultz-Dale bath. Is this effect of normal serum due to complement or is it due to some other factor in the serum, probably a protein? An experiment was then designed to study the "schlepper" action of normal serum. Normal human serum (prior to the addition of M.C.) was subjected to inactivation (by heating to 56°C. for thirty minutes) which would destroy fractions C_1 and C_2 of complement, or to the addition of guinea pig complement (which would supply fraction C_3), or to both. M.C. was then added to the treated and untreated normal serum and these, together with the carcinoma supernatant, were used to release the reactions in horns from guinea pigs actively immunized against M.C. This experiment was performed in collaboration with Dr. P. Krag of the Statens Serum Institute in Copenhagen and the results are recorded in Table 5.

To clarify this immunologic relationship between M.C., the carcinoma sediment, and its supernatant, these various antigens were used to release the reactions in 117 pigs immunized with carcinoma sediment and M.C. The animals were sacrificed at different times after immunization (Table 6).

To understand this relationship further, it was necessary that it should be studied not only in serum but in tissues. Since positive reactions to tests for M.C. can occur even in the serum of some so-called "healthy" persons, is there any evidence to show that M.C.-like

TABLE 1

Results of Schultz-Dale Test in 67 Cases of Proved Tumors when Carcinoma Sediment (3–10,000 rpm), Carcinoma Supernatant (after 10,000 rpm), and Methyl-Cholanthrene Were Used as Immunizing Antigens for Guinea Pigs

Cases	Carcinoma Sediment (3–10,000 rpm); Colon, Cervix & Lung		Methyl-Cholanthrene (M.C.)		Carcinoma Supernatant (after 10,000 rpm); Colon, Cervix & Lung	
	Pos. Reactors	Total	Pos. Reactors	Total	Pos. Reactors	Total
Malignant melanoma						
Total	4	4	1	1	2	2
Carcinoma:						
Breast	4	5	6	7	4	4
Colon					1	1
Liver			2	2		
Lung	3	4			1	1
Prostate					3	3
Skin	1	2	2	3	3	3
Stomach	1	1			3	3
Tongue			1	1		
Vulva	1	1				
Total	10	13	11	13	15	15
Sarcoma:						
Fibrosarcoma	0	1				
Lymphosarcoma			4	4		
Chondrosarcoma	1	1			3	3
Reticulum-cell sarcoma			1	1		
Total	1	2	5	5	3	3
Lymphoma-leukemia						
Lymphoma	1	1	1	1	1	1
Leukemia	1	2			2	2
Total	2	3	1	1	3	3
Benign tumors	1	1			1	1
Grand Total	*18 (78%)*	*23*	*18 (90%)*	*20*	*24 (100%)*	*24*

antigen is present in the tissues of persons who do not exhibit pathologic evidence of cancer? Furthermore, can reactions be released from guinea pigs immunized with these tissues by adding M.C. to the Schultz-Dale bath?

To answer these questions, supernatants obtained at 18,000 rpm from various homogenates of lung tissue were used to immunize the guinea pigs. The lung tissue was obtained from 3 patients—one with proven carcinoma of the lung (Mr. H.); one (Mrs. F.) who was thought to have carcinoma but in whom autopsy failed to confirm the diagnosis (Table 3); and a young healthy male who died accidentally. Sediment from the suspected carcinoma was also used as an immunizing antigen (Table 4).

TABLE 2

Schultz-Dale Reactions in 44 Subjects Whose Sera Were Tested Simultaneously for Carcinoma and Methyl-Cholanthrene Antigens. (Sera Were Tested as Unknowns.)

Group	No. of Cases	% Positive Reactions with Schultz-Dale Method	
		Carcinoma sed. (3–10,000 rpm) antigen	Methyl-cholanthrene antigen
I. Untreated, pathologically proved cases of carcinoma	21	90.5	95.2
II. Other cases (including other tumors)	10	60.0	80.0
III. Apparently healthy subjects	17	35.1	47.0

RESULTS

Sixty-seven cases of proved tumors (Table 1) were divided into 3 groups. When carcinoma sediment (3,000 to 10,000 rpm) was used as the immunizing antigen, results were positive in 18 of 23 cases (78 per cent); when carcinoma supernatant (at 10,000 rpm) was used, results were positive in 24 of 24 cases (100 per cent); and when M.C. was used, results were positive in 18 of 20 cases (90 per cent).

In another 44 subjects (Table 2) whose sera were tested simultaneously for carcinoma and M.C.-like antigens, 90 per cent of 21 untreated and pathologically proven cases of carcinoma showed a positive reaction for carcinoma antigen, and 95 per cent for M.C.-like substance. Of 10 patients with other diseases and other tumors, 60 per cent showed a positive reaction for carcinoma antigen, and 80 per cent for M.C.-like substance. Of the 17 "apparently healthy" subjects 35 per cent showed positive reactions with carcinoma, and 47 per cent with M.C.

In Tables 3 and 4 are listed the studies of antigenic relationships between M.C. and M.C.-like substances in the lung tissues of 1) Mrs. F., clinically suspected of having carcinoma but in whom none was found at autopsy, and 2) Mr. H., in whom carcinoma of the lung was confirmed at autopsy. It is apparent that the lung-tissue supernatants at 18,000 rpm behaved similarly in both of these cases. M.C. in normal serum released the reaction in both, indicating the presence of an M.C.-like substance in both lung-tissue supernatants. This abnormal component could not be demonstrated in the supernatant from lung tissue of a young healthy male who died accidentally. Furthermore, it was also found in other tissues of Mrs. F., such as the cervix.

Similar results were obtained when sediment obtained at 3 to 10,000 rpm from Mrs. F's lung homogenates was used as an immunizing antigen. M.C.-like substances were detected in this experiment but to a lesser extent than with the supernatant (the mean Contraction Index was .38 for the sediment as compared with .44 for the supernatant). With M.C.-immunized pigs, the mean C.I. was 1.0.

These reactions with M.C. are specifically immunologic, since they exhibit desensitization, *i.e.*, a positive reaction followed by a negative one upon repeated contact with the same uterine horn at the same dosage level. There was one interesting difference. In the case of proved carcinoma of the lung (Mr. H.),

TABLE 3

Some Antigenic Relationships as Revealed by the Schultz-Dale Test Between Methyl-Cholanthrene(M.C.), M.C.-Like Substance in Tissues and Carcinoma Antigens

Expt., March 1, 1956				Expt., March 2, 1956			Expt., March 3, 1956		
Releasing Antigen		Immunizing Antigen to G. Pigs		Releasing Antigen		Immunizing Antigen to G. Pigs	Releasing Antigen		Immunizing Antigen to G. Pigs
Type	Amt. in ml.	Mrs. F. "normal" lung supernat. (18,000 rpm)	Mr. H. antigen 210 Ca lung supernat. (18,000 rpm)	Type	Amt. in ml.	Mrs. F. "normal" lung supernat. (18,000 rpm)	Type	Amt. in ml.	Mrs. F. "normal" lung supernat. (18,000 rpm)
Normal serum	.5	(.24)§1	(1.0)1*	Normal serum	.3	(1.0)1*	Normal serum	.3	(.73)1*
Normal serum	.5	0	0	8x ↓			8x ↓		
				Normal serum	.3	0	Normal serum	.3	0
Chondrosarcoma, Moses 18407	.5	(.76)1*	(.92)1*						
Normal serum	.5	0	0	Sera from patients			M.C. (0.2 mg.) in normal serum 2x	.2	(.54)1*
Ca stomach, Ubanski 18419	.5	(.76)1*	(.68)1*						
Normal serum	.5	0	0	M.C. (0.2 mg.) in normal serum	.2	(.3)2*	M.C. (0.2 mg.) in normal serum 2x	.2	(.36)2
Ca breast, Chambers 18439	.5	(.57)1*	(.44)2*						
				M.C. (0.2 mg.) in normal serum	.2	0			
Normal serum	.5	0	0						
Normal serum + M.C. (1 mg.)	.5	(.47)1	(1.0)1*				Sera from patients		
Normal serum	.5	(.95)2*	0	Histamine	10 r	(1)1*			
Normal serum	.5	0	0				Histamine	10 r	(1.0)1*
Histamine	10 r	(1.0)1*	(1.0)1*						

§ Figures in parentheses represent contraction index (C.I.). The numbers 1 and 2 outside parentheses indicate time of contraction, whether in the first or the second half of the run. The asterisk, when added, indicates a strong maintained reaction.

TABLE 4

Some Antigenic Relationships as Revealed by the Schultz-Dale Test Between Methyl-Cholanthrene (M.C.), M.C.-Like Substance in Tissues and Carcinoma Antigens

Expt., February 23 & 24, 1956			Expt., March 5, 1956		
Releasing Antigen		Immunizing Antigen to G. Pigs	Releasing Antigen		Immunizing Antigen to G. Pigs
Type	Amt. in ml.	M.C. (0.2 mg.) with adjuvants	Type	Amt. in ml.	Mrs. F. "normal" lung, sed. III-B (3–10,000 rpm)
		A			
Normal serum	.3	(.44)§1	Normal serum 1x	.5	(.80)1*
↓		↓	↓		↓
Normal serum	.3	0	Normal serum 1x	.3	0
Sera from patients tested			Normal serum + M.C. (0.3 mg.)	.3	(.61)1*
M.C. (0.2 mg.) in Tyrode	.2	0	Normal serum + M.C. (0.3 mg.)	.3	0
M.C. (0.2 mg.) in normal serum	.2	(1.0)1*	Sera from patients tested		
Histamine	10 r	(1.0)1*	Histamine	10 r	(1.0)1*
		B			
Normal serum	.5	0	Normal serum	.5	(.54)1*
			↓		↓
Sera from patients tested			Normal serum	.2	0
M.C. (0.2 mg.) in Tyrode	.2	0	M.C. (0.1 mg.) in normal serum	.1	(.08)1
M.C. (0.2 mg.) in normal serum	.2	(1.0)1*	+ normal serum	.1	(.16)1
			Normal serum	.2	(1.0)1*
			Normal serum	.2	0
Histamine	10 r	(1.0)1*	Histamine	10 r	(1.0)1*

§ Figures in parentheses represent contraction index (C.I.). The numbers 1 and 2 outside parentheses indicate time of contraction, whether in the first or the second half of the run. The asterisk, when added, indicates a strong maintained reaction.

repeated additions of sera from proved cases of cancer produced partial desensitization of the uterine muscle to cancer antigens but not to M.C., indicating the presence of two immunologically related but distinct entities—carcinoma and M.C. antigens. In our clinically suspect but pathologically negative case (Mrs.

TABLE 5

Treatment of M.C.-Containing Serum Before Its Use to Release Reaction in Uterine Horns from Guinea Pigs Actively Sensitized with M.C.

Releasing Antigen			Fresh Serum + Complement		Fresh Serum		Inactivated + Complement		Inactivated	
Type	Amount in ml.	Complement (ml.)	Pig No. 424	Pig No. 425	Pig No. 424	Pig No. 425	Pig No. 424	Pig No. 425	Pig No. 424	Pig No. 425
Normal serum	.5		0	0	0	0	0	0	0	0
Normal antigen	.2		0	0	0	0	0	0	0	0
M.C. in normal serum	.2	.05	(35)§2	(5)1	0	(5)2	(30)1	0	0	0
	.2	.1	(45)3	(14)1	0	(25)3†	(41)1	(38)1*	(24)2	0‡
	.4	.01	0	(15)1	(43)1*		(40)1	(9)2	(22)2	
	.4	.01		(35)1*	0		(44)1	(9)1	0	
	.4	.01		(24)1			0			
				(30)1*						
				(30)1*						
Carcinoma supernatant	.2	0	(30)1		(45)1*		(50)1*		(63)1*	
	.2	0	0		0		(50)2*		0	
	.2	0					(50)2*			
	.2	0					0			
Histamine			(52)1*	(40)1*	(45)1*	(49)1*	(52)1*	(46)1*	(64)1*	(50)1*

§ Figures in parentheses represent height of contractions in mm. The numbers 1 and 2 outside parentheses indicate time of contraction, whether in the first or the second half of the run. The asterisk, when added, indicates a strong maintained reaction.

† When complement was added, contraction (46)1*; complement alone, (40)1, (14)2.

‡ When complement was added, contraction (47)1*; complement alone yielded negative result.

F.), desensitization of the uterine muscle to cancer antigens was also followed by desensitization to M.C., indicating the presence of one main component, M.C.

It may be noted from Table 4 that M.C. in Tyrode did not release the reaction but that M.C. in normal serum did, showing that M.C. behaves as an incomplete antigen or a "hapten" and that it requires the presence of a normal serum component to manifest its antigenicity. This "schlepper" action of normal serum on M.C. is due to something other than complement (Table 5), since even after the serum containing M.C. was inactivated (by heating to 56° C. for thirty minutes), it still was able to release the reaction in a Schultz-Dale bath containing uterine segments from one of the guinea pigs actively immunized with M.C.

Results shown in Table 6 indicate that in guinea pigs immunized to both carcinoma sediment and M.C., antibodies to the carcinoma supernatant (after 10,000 rpm) are more constantly found than to either M.C. or the carcinoma sediment. Thus in guinea pigs immunized with carcinoma sediment, reactions were released by carcinoma supernatant in 76 per cent of cases (16 of 21) as compared with 14 per cent (2 of 14) for carcinoma sediment. Similarly in M.C.-immunized guinea

TABLE 6

Effect of Carcinoma Sediment and Supernatant and of Methyl-Cholanthrene (M.C.) in Releasing the Schultz-Dale Reactions in 117 Uterine Segments from Guinea Pigs Immunized with Carcinoma Sediment and M.C.

Weeks after Immunization	Antibodies Formed Against							
	Carcinoma-Treated G. Pigs				M.C.-Treated G. Pigs			
	Antigen for Releasing Reaction							
	Carcinoma sed.III-B (3–10,000 rpm)		Carcinoma supernatant (after 10,000 rpm)		M.C. in normal serum (1 mg. per 10 ml.)		Carcinoma supernatant (after 10,000 rpm)	
	Uterine horns tested							
	Pos. reactors	Total	Pos. reactors	Total	Pos. reactors	Total	Pos. reactors	Total
3					7	8	4	4
4					0	7	5	7
5								
6								
7					0	14	10	14
8			7	7				
9					1	14	14	14
10								
11								
12	0	7	2	7				
13								
14								
15	2	7	7	7				
Total	2	14	16	21	8	43	33	39
Percentage positive	(14%)		(76%)		(19%)		(85%)	

pigs, reactions were released in 85 per cent of cases (33 of 39) as compared with 19 per cent (8 of 43) when M.C. in normal serum was used.

A more significant finding is the relationship of the appearance of these different antibodies to the time of immunization. In the early phase of immunization, guinea pigs injected with M.C. develop antibodies to M.C. to a greater degree than antibodies against carcinoma supernatant. On the fourth week of immunization and thereafter, antibodies to M.C. disappear and are replaced by antibodies to carcinoma supernatant.

Similarly in our previous experiments (1), using sediment for immunization, antibodies to carcinoma sediment were most prevalent between the third and fourth week following immunization. After the fourth week, these antibodies disappeared for the most part. This may be seen in Table 5, which also shows that, in guinea pigs immunized to carcinoma sediment, antibodies to carcinoma supernatant persist much longer (fifteen weeks or more).

DISCUSSION

We know that carcinogenic polycyclic hydrocarbons possess a specific tumor-inhibiting action (4). Is this due to a specific antibody? Creech and Peck (5) showed that carcinogens are indeed capable of haptenic modification and that artificial protein conjugates stimulate specific antibody formation. Creech, Havas and Andre (6), using precipitation techniques, further established the antigenicity of carcinogen protein conjugates. We have now produced more evidence of the antigenicity of M.C. when it is used as an immunizing antigen with Freund's adjuvants. It is also evident that M.C. behaves as a hapten (an incomplete antigen) when used to release the reaction in the uterine horns of pigs immunized with M.C.

The detection of M.C. by the Schultz-Dale test provides a good method to study the distribution of M.C. and M.C.-like substances in the sera and tissues of cancer patients and normal persons.

The presence of M.C.-like substances in the sera of apparently healthy subjects raises some extremely significant questions regarding the cause and prevention of cancer. Do such M.C.-like substances occur in other tissues as well? Is cancer more apt to develop in the person with M.C.-like substances in his serum? If so, could we not do something during this very early phase to prevent the development of cancer?

The finding of M.C.-like substances in the lung-tissue homogenates of Mr. H. (proved carcinoma of the lung) is not surprising, nor is their absence in the lung-tissue homogenates of the young man who died from an accident. Their presence in the lung-tissue homogenates of Mrs. F. (cancer clinically positive but pathologically negative) is of even greater interest. Apparently the mere presence of a carcinogen or an M.C.-like substance will not of itself induce cancer; in addition, certain host factors must be disturbed.

This could partially explain the positive Schultz-Dale reactions in some apparently healthy persons. However, this statement must be qualified. The work on unknown sera reported in Table 2 was performed under experimental conditions which were not optimal. The sera were treated as coming from separate subjects. The worker did not know that the serum from each subject was divided into halves, each of which was given a separate number. Thus one uterine horn was used to test many samples. This technique is fairly adequate when sera from various subjects are used, but is less reliable when the same serum is retested several times.

Thus desensitization of the guinea pig uterine horn to a given antigen could easily result from repeated additions of a single serum, and a false negative reaction would be obtained. Conversely, an unrelated antibody, if present with its antigen, could become fixed to the uterine horn on initial contact, so that repeated addition of the same serum containing the unrelated antigen to the same horn might induce a false positive reaction. For these reasons, the values in this particular experiment may not be as accurate as the others, but they indicate a significant trend.

The fact that the M.C.-like substance was extracted from more than one tissue of the pathologically negative case (Mrs. F.) suggests that it probably had reached the blood stream for dissemination. Recently Falk, Miller and Kotin (7) reported on the elution of 3,4-benzpyrene and related hydrocarbons from soot by plasma proteins. The opinion was expressed that phagocytosis produced an abnormally high local concentration of soot particles followed by the elution of benzpyrene from the soot by the intracellular proteins of desorbed polycyclic aromatic hydrocarbons. This provides a favorable environment for the biologic activity of carcinogenic hydrocarbons. It seems logical that these hydrocarbons, having reached the intracellular proteins, would soon reach the blood as a result of the dynamic interaction between tissue and blood proteins.

Whatever the reason, this time lapse between the accumulation of M.C.-like substances in the tissues and the initial formation of a tumor could provide an opportunity to break a chain of events which, unchecked, could ultimately result in a neoplastic growth.

The immunologic relationships between M.C., carcinoma-supernatant antigen and carcinoma-sediment antigen are of great interest. Carcinoma-sediment antigen was present to a lesser extent in the 67 tumors studied (Table 1) than was M.C. or carcinoma-supernatant antigen. Moreover, these antigens were found to a much greater extent in patients with carcinoma than in those with other tumors and in apparently healthy persons.

The carcinoma-sediment antigen used was described earlier (3) as a common antigen for all tumors. However, in this study, it retained some degree of specificity, so that it was a better agent for detecting its own type of tumor than were the other tumor antigens. These results are in agreement with our earlier work.

But what is the relationship of M.C. and cancer-supernatant antigen to this common carcinoma-sediment antigen which we were able to identify in all the tumors tested?

Table 5 affords a possible clue to this relationship. Since the presence of an antibody is a good indication of the persistence of an antigen in the tissues, we may conclude that carcinoma-supernatant antigen remains longer in the tissues of the guinea pig than does either M.C. or carcinoma-sediment antigen.

It is, therefore, not surprising that only 2 of 7 (28 per cent) of the guinea pigs immunized and tested with carcinoma-sediment antigen were still sensitized fifteen weeks after immunization. When tested with supernatant antigen, 7 out of 7 (100 per cent) were still sensitized after fifteen weeks. Similarly, only 1 of 14 (7 per cent) among the guinea pigs immunized and tested with M.C. were still sensitized nine weeks after immunization. However, when tested with supernatant antigen, 14 of 14 (100 per cent) were still sensitized. Yet 7 of 8 (87.5 per cent) of these same M.C.-immunized pigs gave positive reactions when tested with M.C. in the third week of sensitization but not later.

What happens to M.C., a powerfully carcinogenic hydrocarbon, during the fourth week of immunization? What happens to the carcinoma-sediment antigen at the same time? Why should carcinoma-supernatant antigen appear in both groups and persist for such a long time?

Wiest and Heidelberger (8) showed that, following topical application of 1:2-5:6-dibenzanthracene-9,10-^{14}C to the skin of mice, irreversible binding takes place between the carcinogen (or its metabolites) and the nucleoproteins, particulate or soluble proteins, but not with nucleic acids. Could the aromatic hydrocarbon at this time attach itself to a protein carrier, thereby changing its antigenicity somewhat and appearing as the immunologically active carcinoma-supernatant antigen?

Recently Makari (9) described the polysaccharide nature of cancer antigens. One hypothesis is that M.C., the carcinogenic hydrocarbon, can be directly converted into the specific polysaccharide hapten of the carcinoma supernatant by the action of certain enzymes through a process of polymerization, and that this polysaccharide hapten may then attach itself to a protein carrier to become a full antigen analogous to the carcinoma-supernatant antigen.

On the other hand, it may be that the presence in the tissues of a carcinogen such as M.C. indirectly stimulates the production or release of specific polysaccharides. If so, these may then attach themselves to protein carriers to become tumor antigens. Since carcinogenic ability is not restricted to aromatic hydrocarbons, but is possessed by a great range of chemical, biologic and physical agents, this possibility is much more likely. Astaldi and Verga (10) showed that the polysaccharide content of human lymphocytes and neutrophils is increased when they are irradiated in homologous serum.

Asboe-Hansen *et al.* (11) showed that on the fourth to sixth days following injection of Rous sarcoma virus into the pectoral muscles of 2-month-old chickens, histologic preparations showed accumulation of mast cells and formation of intercellular mucopolysaccharides.

Perhaps the various carcinogenic agents share the ability to stimulate the formation of abnormal polysaccharides which may in turn induce cancer by means of excessive and abnormal stimulation of the reticuloendothelial lymphocyte system, or by inducing tolerance so that masked viral agents are allowed to become active without interception by the host defenses. In support of the first possibility is the excessive stimulation by polysaccharide antigens leading to immunoparalysis, as described by Felton and Ottinger (12). In support of the second possibility is the recent finding by Harris and Simons (13) that Rous sarcoma agent was made to "take" in turkeys given injections of chicken blood immediately after hatching. The antigen conferring tolerance is also present in guinea pig blood, hog gastric mucin, and Group A human corpuscles. It is thought to be blood Group A substance (which is itself a polysaccharide).

The reactions of various species to carcinogenic hydrocarbons differ widely, the guinea pig having virtually no skin tumor response (14). This state of resistance may reflect the ability of the guinea pig to completely rid itself of M.C. in its tissues, and it could also explain the persistence of M.C. in both of our patients with tumors and the apparently healthy subjects. Might the failure of some persons to completely eliminate M.C.-like substances from their tissues be the basis of their susceptibility to cancer?

Whatever the mechanism involved, the detection of M.C.-like substances in

the serum of apparently healthy subjects is significant. These M.C.-like substances must reach a certain threshold in the tissues before they appear in the blood. Furthermore, since this stage of high carcinogen level in the tissues precedes the development of cancer (as demonstrated by animal experiments), and since it does not necessarily lead to cancer (as is shown by Mrs. F. in this study), a golden opportunity presents itself for the possible prevention of the disease. Having detected a high threshold level of M.C.-like substances in the blood, it might be possible to stop or even to reverse the process of carcinogenesis by preventing further exposure to known or suspected carcinogens, thus decreasing the load which the host defenses have to carry. This might be done by changing the environment (*e.g.*, removal from atmospheric pollution or exposure to radiation) and changing food and other habits (*e.g.*, excluding dyes from food, or ceasing to smoke).

This phase would be amenable not only to preventive measures but also to a direct attack on carcinogens by means of chemoprophylaxis. The aim of this paper is to stimulate thinking along these lines and to urge further exploration of this concept.

SUMMARY

The Schultz-Dale method has been modified to permit detection of substances antigenically similar to methyl-cholanthrene (M.C.) in the serum of patients with tumors and the serum of some apparently healthy persons. This was accomplished by using carcinoma supernatants (at 10,000 and at 18,000 rpm) and M.C. to immunize guinea pigs.

An attempt has been made to explain some relationships between carcinogens, such as M.C., and the polysaccharide carcinoma antigens. The various carcinogens (whether chemical, physical or biologic) all share the ability to stimulate the production or release of specific polysaccharides. These may, in turn, induce cancer by means of excessive and abnormal stimulation of the reticuloendothelial lymphocyte system, or by inducing tolerance so that masked viral agents are allowed to become active without interception by the host defenses.

The detection of M.C.-like substances in apparently healthy persons may prove to be a significant step toward the prevention, and perhaps the chemoprophylaxis, of cancer.

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This work was conducted at the University of Texas.

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HOST-TUMOR ANTAGONISM. XIII. SARCOMA OF THE SOFT TISSUES TREATED BY BACTERIAL TOXINS: SUCCESSFUL SERIES*

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Much has been said of the phenomenon of "spontaneous" regression of cancer. It has different meanings for different authors. Everson and Cole (52b)[1] defined it as the partial or complete disappearance of a malignant tumor in the absence of all treatment, or in the presence of therapy which is considered inadequate to exert a significant influence on neoplastic disease.

If such regressions were truly spontaneous, they might simply be noted as esoteric phenomena and evoke little further discussion. It happens, however, that the regressions reported in the literature are not truly spontaneous, but are almost always associated with certain unusual circumstances such as acute concurrent infection, inflammation, fever or bacterial toxin therapy. If a common denominator could be found in these cases, a first step in the solution of a giant riddle might be made.

The purpose of this review is to analyze the effect of bacterial toxin therapy on patients with sarcoma of the soft tissues. (The data relating to the effect of infections and bacterial toxins on all types of neoplasia will appear in subsequent reports.) It is hoped that the analysis of factors influencing success and failure in the following 186 cases will lead to greater knowledge and more effective use of the method.

The treatment of malignant tumors by bacterial toxins is based on the fact that neoplasms have been known to regress during acute bacterial infections, principally erysipelas, but also acute tuberculosis and smallpox. The inhibitory action was often powerful enough to cause complete regression, and in some instances there were no recurrences.

Busch (4) is usually credited with being the first physician to invoke the help of erysipelas infection to cause the regression of cancer. However, Collis (44a) had discussed this idea in 1864. He emphatically stated that when a patient recovers from a severe attack of erysipelas after the removal of a cancerous part, there is less likelihood that the cancer will recur.

In 1868 Busch (5) reported on the dramatic regression of inoperable sarcoma in 2 patients who had contracted erysipelas. He attempted to induce erysipelas in

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[1] The references are listed at the end of Study XIV, which will be published in the September issue.

certain patients having malignant disease, but was largely unsuccessful. The etiologic organism of erysipelas was discovered in 1882 by Fehleisen (53a), who promptly used it for the induction of erysipelas in cancer patients.

After noting that Busch had tried to treat inoperable malignant neoplasms of the lymph glands by means of erysipelas, Fehleisen was successful in infecting a patient by placing her in a bed in which patients with open wounds usually contracted erysipelas. The desired effect was obtained. The tumor, which was an extensive lymphosarcoma of the neck, disappeared except for a small portion; this portion, however, again became enlarged. The treatment was only partially satisfactory, but it encouraged further trials. Fehleisen reported the results in a personal series of 7 cases in which he attempted to induce erysipelas. There were some partial regressions, and in 1 case of thrice-recurrent mammary cancer there was complete regression.

W. B. Coley became interested in the phenomenon when an inoperable lymphosarcoma of the neck, which had recurred postoperatively three times, regressed following an attack of erysipelas. Beginning in April 1891, Coley (8) attempted to produce erysipelas as a therapeutic agent in 10 patients with inoperable malignant lesions. It was difficult to induce an attack, and often dangerous when it finally occurred. He tried cultures of *Streptococcus erysipelatis* sterilized by heat or filtration, but these were found to be weak and ineffective. A short while later he learned that the toxins of *Bacillus prodigiosus* could increase the virulence of other organisms, if the association occurred during the proliferative stage (89a).

Various mixed toxins were developed under Coley's direction, some of which were weak, and others effective (77, 78, 80). A considerable number of patients are alive today who recovered from inoperable neoplasms after having been treated with a toxin mixture by Coley or under Coley's direction. Some of the so-called spontaneous regressions of cancer have been in patients who were treated with Coley's toxins.

Coley usually employed intratumoral injections of toxins in his early work, and these apparently produced the best results. Intramuscular injections were relatively ineffective. Intravenous injections were more effective than those by the intramuscular route, and were better borne by the patient (77).

Fowler (54), an enthusiastic observer and one of the most brilliant surgeons of his time, stressed the importance of producing definite reactions (at least two or three well marked reactions in a week) and continuing therapy for three or four months. He was especially interested in the fact that fever due to erysipelas or to the mixed toxins should prove destructive to neoplastic cells, whereas fever due to other diseases did not have this effect.

Recently Nauts, Fowler and Bogatko (80) critically analyzed 30 of 270 or more inoperable cases of malignant tumor in which complete regression was obtained. For no other therapy have so many regressions been claimed in inoperable cases.

The question arises as to how acute infection, acute inflammation, fever or bacterial toxin therapy may exert apparently beneficial effects on patients with cancer. It is known that neoplastic cells are more sensitive to heat than are nor-

mal cells (65). Moreover, infections or their toxins may activate or mobilize various cells, tissues or systems in the body which affect tumor immunity, and which may not be functioning normally in cancer patients.

Beebe and Tracy (1c) injected bacterial filtrates, including filtrates of *Str. pyogenes* and *B. prodigiosus*, into dogs bearing transplanted lymphosarcomas. In many of the dogs, softening of the tumors occurred and sometimes there was complete regression. Shwartzman (97a) noted that when bacterial filtrates (especially of Gram-negative organisms) were injected into the skin of normal rabbits, and this was followed in from four to forty-eight hours by an intravenous injection of the same or different filtrates, an intense reaction occurred in the skin at the site of the original cutaneous injection. The local site at first became hemorrhagic and later usually became necrotic. The cause remained obscure. The process apparently was not due to local blockade of the reticulo-endothelial cells, or to inflammation or increased capillary permeability.

The work of Gratia and Linz (54b) applied the Shwartzman reaction directly to the chemotherapy of tumors. These Belgian investigators injected filtrates of *B. coli* directly into transplanted liposarcoma in guinea pigs. Twenty-four hours later, portions of the same filtrates were injected intravenously, resulting in extensive hemorrhage and necrosis in the tumor masses but not in other parts of the animal. In other experiments, the same effect on the tumor was observed after injecting the filtrate intravenously, without the preceding injection of the tumor. Gratia and Linz thought that this reaction was possible because of a prior sensitization of the tumor. They postulated that the liposarcoma had been sensitized spontaneously by pre-existing micro-organisms; subsequently finding none, they inferred that a virus had sensitized the tumor, and that cancer was caused by a virus. The inferences may not have been correct, but the data seemed valid. Shwartzman and Michailovsky (97b) confirmed this phenomenon, using a different filtrate and a different animal.

The acute inflammatory reaction is another important factor in the host's resistance to neoplastic diseases. Southam and Pillemer (98) found that the implantation of cancer cells into normal volunteers elicited a marked local inflammatory reaction and rapid rejection of the transplant. In patients with advanced cancer, the initial inflammatory reaction was minimal and growth of the implanted cells occurred at almost all sites.

It may be significant that the histamine liberated by acute inflammation appears to be a physiologic activator of the reticulo-endothelial system (62a). It is well to remember that an erysipelas infection, in addition to the fever it invokes and the toxins it produces, is accompanied by the most acute inflammatory reaction of any type of infection. By far the largest number of dramatic regressions of inoperable cancer occurred in the patients who contracted erysipelas. Was this due to the fact that these patients were still able to elicit a profound inflammatory reaction to their infection, or merely to the fact that they were lucky enough to contract this type of infection?

Southam and Pillemer (98) found that none of the factors which are thought to be related to body defense mechanisms were demonstrably deficient in the 17

cancer patients they tested, except for properdin. Properdin is a euglobulin in the blood serum, discovered by Pillemer in 1954; in the presence of complement and magnesium, it inactivates bacteria and viruses (87a). The properdin system may play a role in resistance to cancer. A single small injection of bacterial polysaccharides appears to stimulate the production of properdin, whereas x-ray irradiation inactivates it. In mice, the administration of polysaccharides from normal and neoplastic tissues can depress serum properdin levels. This suggested to Southam and Pillemer that a large mass of cancer tissue may of itself absorb properdin or liberate into the circulation tissue polysaccharides which combine with properdin, thus depressing properdin levels.

The present report consists of all the microscopically proved cases of operable and inoperable sarcoma of the soft tissues, other than lymphosarcoma, in which toxin therapy (Coley toxins) was administered. The cases have been grouped according to the stage of the disease at the time toxins were begun, and the type of toxin used. Nine of the successful results in inoperable cases were reported in detail in the review of Nauts, Fowler and Bogatko (80) as Cases 1, 2, 3, 4, 8, 20, 23 and 28. The details of the 186 case histories briefly abstracted in the present report are available for study at the New York Cancer Research Institute.

Even if the administration of Coley toxins were associated with the regression of only one cancer, it would be worthwhile to find the possible explanation for this phenomenon.

The case histories were taken from the published reports of the indicated authors, relevant correspondence between those authors and Dr. William B. Coley, and Dr. Coley's office records and published material. (A few of the cases had not yet been published. These histories were obtained by the New York Cancer Research Institute from the attending physicians or hospital records.)

In addition, because a number of the patients are still alive, the state of their present health was determined by personal interview, correspondence with the patient, or with his present physician.

The cases were divided into operable or inoperable groups, based on the opinion of the surgeon who had charge of the patient. It was not possible to make this division a very strict one, and undoubtedly there was some overlapping. However, it probably indicated in rough fashion the severity and spread of the lesion in each patient.

SERIES A

70 CASES OF INOPERABLE SARCOMA OF THE SOFT TISSUES (OTHER THAN MALIGNANT LYMPHOMA) SUCCESSFULLY TREATED BY COLEY TOXINS

The diagnosis was confirmed by microscopic examination in each instance. The name in parentheses following the case number refers to the physician or surgeon handling the case. The abstracts are listed chronologically according to the type of toxin used and the date of the first injection. At the end of each abstract the bibliography reference numbers indicate where more details may be found.

Toxins, Type IV or V (10 cases)

These were filtered preparations. For a brief description of the various formulae used in making Coley toxins see references 77 and 80.

Years traced after onset

1. (Coley): J. F. F., male, aged 16; inoperable spindle-cell sarcoma (5 x 6½ inches), entire thickness of abdominal wall, attached to pelvis and involving bladder wall. Patient's general condition poor; micturition involuntary; confined to bed most of time. Onset in October 1892; exploratory laparotomy January 24, 1893. Toxins injected into tumor for six months; *steady decrease in size, which continued after toxins were stopped; complete regression;* no recurrence; patient in perfect health. Sudden death on February 28, 1919, from chronic myocarditis, twenty-six years after onset of sarcoma. First case of any type of cancer to receive Coley's *mixed* toxins. (9, 11, 12 (p. 70) 21, 22, 29, 41, 73, 80, 102.) 26

2. (Coley): W. S. G., male, aged 15; twice recurrent inoperable angiosarcoma of nasal septum and nasopharynx with onset in July 1891; tumor removed by Abbé, but promptly recurred; Abbé operated again, taking away most of left superior maxilla; prompt recurrence of considerable size; 2 electrolytic treatments (unsuccessful). June 1893, toxins injected in region of tumor; marked reactions; *uninterrupted improvement; tumor completely disappeared.* No further recurrence; patient remained in good health, married, and had 5 children. A small epithelioma on the back of his neck was excised in 1950. Died from severe heart attack on January 15, 1951, aged 75. (41, 42, 81.) 59½

3. (Coley): Mrs. E. J. L., aged 29; extensive inoperable fibrosarcoma of abdominal wall filling lower left quadrant; onset in April 1893; patient cachectic; exploratory operation; no attempt at removal (small piece removed for biopsy); prognosis grave. October 1893, toxins injected directly into tumor daily, causing inflammation; large doses, febrile reactions of 101°–102°F.; *improvement evident in two weeks; complete regression in four months;* no recurrence. Patient died from heart failure in 1918. (12, 13, 14, 29, 41, 80, 89.) 25

4. (Johnson): T. C., male, aged 16; inoperable spindle-cell sarcoma involving tonsils, palate, roof of mouth, nasopharynx, pillars of fauces, part of pharyngeal wall, whole base of tongue, epiglottis and upper larynx; uvula entirely destroyed; cervical glands enlarged. Patient had lost much weight and strength; deglutition difficult; nasal breathing impossible; prognosis hopeless. Onset early 1893; untreated. Beginning October 31, 1893, toxins were given for eight months intramuscularly (legs, arms); febrile reactions, 99° to 103°F.; *steady slow improvement; deglutition easy in two weeks; extensive growth completely disappeared, partly by absorption, partly by necrosis.* Patient gained 22 pounds; stronger; no recurrence; alive and in very good health June 1915; not traced thereafter. (12, 24, 31, 41.) 22

5. (Coley): Miss M. L., aged 35; inoperable retroperitoneal round-cell sarcoma, apparently recurrent from a primary growth in the uterus; recurrent after hysterectomy; pain in back and abdomen. Onset in 1889; second operation attempted but abandoned. Beginning January 12, 1894, toxins were given for eight weeks intramuscularly in the thigh; *considerable regression;* upon exploratory celiotomy, tumor was still the size of a goose egg and inoperable. Toxins were resumed and given every forty-eight hours; *tumor did not disappear until several months after toxins were stopped.* No further recurrence when last traced in 1917. (29, 41, 42, 73.) 28

6. (Coley): F. K., female, aged 16; extensive infiltrating inoperable fibrosarcoma of tendon sheath over metatarsal bone, recurrent in stump, leg, thigh, gluteal regions. Onset in 1889; excision 1889; recurrence three years later; Syme's amputation; further recurrence in stump, popliteal space; also inguinal lymphadenopathy. At third operation, popliteal recurrence not entirely removed; stump recurrence untouched. In March 1894, treated with toxins; *complete regression;* patient gained 17 pounds. Fur-

Years traced after onset

ther recurrence in gluteal region in October 1895; toxins caused *diminution;* later mid-thigh amputation; toxins were resumed, given with intervals of rest, for three years; *no further recurrence.* The patient was in excellent health in 1936. (12, 13, 14, 14a, 16, 29, 34, 43 (Case 1), 73.) 47

7. (Coley): Mrs. M. S., aged 29; very large recurrent inoperable fibrosarcoma of the gluteal region and thigh. Onset about 1886; surgical excision in October 1891, when the lesion measured 4 by 6 inches; recurrence in three months; tumor became very extensive and caused much pain; prognosis hopeless. April 7, 1894, started toxins locally for three months; dosage increased to produce marked reactions; *pain ceased but improvement very slow; growth continued to decrease after injections stopped.* April 29, 1899, fibrous remains were excised; no microscopic evidence of malignancy; no further recurrence; patient in very good health. She died on February 2, 1941, from coronary heart disease. (11, 20, 29, 41, 73, 81.) 55

8. (Mynter): C. P., female, aged 12; inoperable spindle-cell sarcoma involving parietal peritoneum, mesentery, pelvic organs and cecum; abdomen enormously distended; micturition involuntary. Onset about March 1894. At laparotomy, 2 quarts of chocolate-colored fluid escaped; specimen from soft vascular growth removed; profuse hemorrhage checked by packing; patient moribund. July 26, 1894, toxins started four days after operation; given daily into upper thigh; no marked reactions; *immediate, steady, complete regression;* (necrotic pieces of tumor sloughed and were evacuated through drainage tube). Patient in good health without recurrence in June 1898; not traced subsequently. No record of death found in period 1898–1954. (28, 34, 77, 78.) 4

9. (Coley): T. J., male, aged 32; thrice recurrent inoperable fibroangioma of upper lip. Onset in 1891; first operation 1892; recurrence; second operation; extensive recurrence with very rapid growth followed third operation. Beginning November 19, 1895, toxins (Type V) were injected into the tumor; *immediate decrease; almost entire disappearance in three weeks;* plastic operation later to restore lip. No further recurrence; patient alive and well in 1903. (13, 16, 41, 76a.) 12

10. (Coley): M. S., female, aged 5; twice recurrent inoperable small round-cell sarcoma of lip. Onset in July 1896, following trauma. Two operations; recurrence of rapidly growing tumor extending from mucous membrane of lip downwards for 1½ inches. February 10, 1897, started injections of toxins into tissues near the tumor; slight reactions; *complete disappearance;* scar tissue then excised; no evidence of tumor remained; toxins given for one year; no further recurrence. Patient married, had 3 children, and was alive and well in 1958. (14a, 20, 29, 39, 81.) 62

Buxton's unfiltered toxins, Type VI (23 cases)

11. (Coley): S. C., female, aged 16; inoperable spindle-cell sarcoma (13 inches diameter) in left scapular region; extensive involvement of entire left chest wall from clavicle to costal margin. Onset in March 1894. Incisional biopsy June 23, 1894; then toxins injected into tumor; fairly marked febrile reactions; *immediate and rapid improvement; complete regression* in nine and a half months, entirely by absorption; as a precaution toxins given for ten months; no recurrence. Patient alive and well in December 1913. (12, 13, 14, 18, 20, 29, 73, 80.) 19½

12. (McArthur): Mrs. D. P., aged 40; recurrent inoperable fibrosarcoma originating in sheath of the tibial muscles of the calf. Onset in 1891. Very radical excision of primary growth, March 30, 1894; recurrence size of walnut; patient 3½ months pregnant when toxins were begun on September 28, 1894; *progressive improvement;* no marked reactions; no unfavorable effects on pregnancy; normal child born at full term; *complete regression of sarcoma;* no further recurrence. Patient alive and well in November 1912. (16, 85a.) 21

Years traced after onset

13. (Packard): Female, aged 39; recurrent inoperable spindle-cell sarcoma of parotid; date of onset not stated; primary growth removed in 1894; recurrence within a year. Beginning in August 1895, toxins injected daily for several months into growth or surrounding tissues; *marked rapid regression;* growth "shrank away to an unoffending node"; further injections failed to dissipate this fibrous stroma, which was dissected out; excellent healing; no further recurrence. Patient in excellent condition in 1898. (20, 41, 29, p. 152.) 4½

14. (Coley and Cobb): Mrs. M. D., aged 40; spindle-cell sarcoma of iliac fossa, size of coconut, involving the ilium and abdominal wall. Onset in May 1895. Exploratory laparotomy; specimen removed. Beginning November 1, 1895, toxins were given by Cobb for six weeks; *complete regression;* a few months later, extensive recurrence filled right lower quadrant; toxins resumed for two months by Coley, causing regression to one fifth former size; injections not given during hot weather; again, recurrence; toxins resumed and continued for seven months; immediate decrease in size; *complete regression;* no further recurrence. Patient alive and well in 1907. (19, 20, 24, 38, 73.) 12

15. (Storrs and Griswold): E. E. F., female, aged 42; inoperable rapidly growing spindle-cell sarcoma of pectoral region and breast; rapid loss of weight and strength. Onset in October 1895; tumor size of orange in two months; biopsy. December 16, 1895, started injections of toxins into tumor; incision and drainage to evacuate necrotic tumor tissue; *complete regression* in three and a half months; no recurrence. Patient in good health; married. Forty-five years later basal-cell epithelioma developed on nose. Patient died from bronchopneumonia and arteriosclerosis on May 2, 1943, at the age of 89. (15, 16, 17, 20, 24, 29, 41, 77, 80, 102.) 47½

16. (Nicholson): Mrs. J. R. C., aged 47; inoperable twice recurrent spindle-cell sarcoma of thigh with extensive involvement of inguinal glands; entire limb edematous. Date of onset not stated. Primary and first recurrent tumor removed surgically; further extensive recurrence; surgery not possible. Beginning in January 1896, toxins given every forty-eight hours for two and a half months; febrile reactions, 101.5° to 103°F.; *complete regression of recurrent tumor, inguinal involvement and edema.* Patient alive and well in July 1899, about three and a half years after toxins were begun. (82a.) 3½

17. (Williams): Mrs. E. Z., aged 37; recurrent inoperable spindle-cell sarcoma of uterus; large growth projected several inches above surface of abdomen. Onset in 1895; exploratory laparotomy March 24, 1896; portion removed for biopsy. Beginning April 4, 1896, toxins injected directly into tumor; very severe reactions (high dosage for intratumoral route); poultices also applied; necrotic tumor tissue drained through sinus 2–3 inches deep in center of tumor; *steady rapid regression; complete disappearance of* extensive hard tumor; no further recurrence. Patient alive and well in 1914. (20, 29, p. 151, 41.) 19

18. (Packard): E. P., female, aged 15; inoperable round-cell endothelial sarcoma of pelvis. Date of onset not stated. Exploratory laparotomy; biopsy. In May 1896, treated with toxins; *rapid local and general improvements; complete regression;* no further recurrence. Patient alive and well in 1906. (29, p. 152, 41.) 10

19. (Packard): Female, aged 55; extensive recurrent inoperable sarcoma inseparably adherent to the abdominal viscera. Date of onset not stated. Primary tumor had been removed previously; fragments of recurrent growth removed at second laparotomy; prognosis hopeless. In May 1896, treated with toxins; *rapid local and general improvement; complete regression;* no further recurrence. Patient alive and well in 1906. (20, 23, p. 182, 29, p. 152, 41.) 10

20. (Roberts): Female, aged 18; round-cell endothelial sarcoma of left ovary, with many secondary nodes in adjacent viscera; ascites. Date of onset not stated; exploratory laparotomy on May 4, 1896; toxins begun soon after; given subcutaneously in

Years traced after onset

abdominal wall steadily for several weeks; *all growths disappeared;* no recurrence or further metastases. Patient later married; was alive and well in 1908. (16, 19, 23, 29, p. 152, 85b.) 12

21. (Zabriskie): Female, aged 43; recurrent extensive inoperable intra-abdominal sarcoma. Onset late in 1895. Primary growth was "size of child's head" when removed; large recurrent tumor in four months; rapid growth. November 1896, toxins given thrice weekly for three months; *marked decrease in size of tumor; remained stationary for a time, then regressed completely* with continued injections (given for twelve months); no further recurrence. Patient alive and well in 1908. (16, 29, p. 155.) 13

22. (Coley): Mrs. B., aged 34; inoperable thrice recurrent mixed round-cell and spindle-cell sarcoma of parotid. Date of onset not stated. Primary growth and first two recurrences removed surgically; further operation inadvisable. January 1897, toxins in small doses; *marked decrease in size; increase in mobility; most of remaining tissue easily excised under ether; found to be fibrous stroma of former growth;* toxins given another three months (total of seven months); no further recurrence. Patient was well when last seen in 1907. (17, 17a, 20, 29, p. 60.) 10

23. (Grindon): Mrs. R. B., aged 50; recurrent inoperable spindle-cell sarcoma in supraclavicular region, involving thoracic wall behind first and second ribs. Onset early in 1897; incomplete operation performed a few days after mass above left clavicle first noted; prompt recurrence; mass soon exceeded its former size. Patient's general condition very poor; bed-ridden. Starting April 15, 1897, 58 injections of toxins were made into tumor and vicinity over a period of six months; marked reactions from beginning of treatment; *complete regression* in four months; regained health; three months after last injection recurrent nodules appeared in neck, breast and axilla; toxins resumed without effect (only 6 doses in eight weeks); several nodules excised in April 1898; toxins then given more aggressively; *remaining growths sloughed and healed;* no further recurrence. Patient died from unrelated causes in 1905. (31, 41, 81, 108a.) 8

24. (Coley and Wright): W. W. L., male, aged 40; twice recurrent inoperable spindle-cell sarcoma of parotid, involving the submaxillary glands. Onset early in 1897; first operation in March 1897; rapid recurrence; two more operations, third incomplete; very rapid growth thereafter. Beginning July 20, 1897, toxins given by Wright for three weeks; little effect except some softening and sloughing of central ulcerated portions; toxins then given aggressively by Coley (daily large doses); *complete disappearance* of tumor in two months; no further recurrences. Patient in perfect health until death on November 22, 1903, following severe hemorrhage from a gastric ulcer. (15a, 16, 16a, 17, 18, 20, 29, p. 98, 102, 113a.) 6

25. (Roberts): Adult (sex not stated); inoperable intra-abdominal sarcoma. Date of onset not stated; exploratory laparotomy, specimen removed. In 1899 treated with toxins; *complete regression.* Patient well and free from recurrence in October 1905. (Roberts had at least two other successes in similar cases.) (29, Case 47 in table.) 5

26. (Coley): Mr. E. S., aged 55; recurrent inoperable small round-cell sarcoma of parotid, highly malignant histologically. Onset in November 1899; incomplete operation on April 5, 1900; prompt recurrence. October 5, 1900, started injections of toxins into tumor four or five times weekly in small doses; moderate reactions; no pronounced change, except slight decrease in size of tumor; increase in mobility during first month's treatment; after another two months of treatment, improvement more marked; *growth disappeared after eight months of treatment;* no further recurrence. Patient died in 1907 of severe herpes involving the Gasserian ganglion; no evidence of recurrence at time of death. (17b, 18, 20, 29, p. 92.) 8

27. (Coley and Mead): Mrs. H. G. L., aged 40; inoperable fibrosarcoma of abdominal wall, involving bladder. Onset in early 1900; exploratory laparotomy on December 19, 1900; several nodules removed for biopsy; toxins begun five days later in

Years traced after onset

daily increasing dosage; given for five months; *complete regression;* no recurrence. Twenty-three years later, primary carcinoma of liver developed, causing death on October 17, 1924 (no toxins given for this neoplasm). (24, 29, 73, 81, 102.) 24

28. (Coley): M. J. H., female, aged 34; extensive inoperable fibrosarcoma of anterior abdominal wall (6½ x 6 inches in diameter), filling entire right iliac fossa. Patient had undergone panhysterectomy for "fibroadenoma" of the uterus in August 1898; onset of fibrosarcoma two years later; pain; mass in region of cicatrix. Exploratory incision April 19, 1901: portion excised for biopsy; two days later toxins begun—20 doses in first sixty days, some into tumor; 12 caused adequate febrile reactions; *growth softened and decreased to less than half its size in eight weeks; after discontinuing toxins, growth increased to former size and became harder.* Toxins resumed October 3, 1901, for six and a half weeks; *at first marked diminution; then no further effect;* cachexia; condition hopeless. Partial removal of tumor on December 27, 1901; 46 x-ray treatments January to June 1902; tumor increased to 15 inches in diameter; patient had *several attacks of fever,* and toxemia lasting few days; *general health then improved* considerably. Total of 136 x-ray treatments in 849 days; complete regression by May 1904; gained 19 pounds; considerable skin damage and ulceration from x-rays; skin-grafts required; later, x-ray cancers developed and were excised. Patient alive and quite well in 1958 at the age of 91. (17a, 18a, 19a, 41, 73, 81, 87a.) 57

29. (Davies): A. G. W., male adult; recurrent inoperable mixed-cell sarcoma of the neck, involving anterior border of sternocleidomastoid muscle and deeper structures. Onset in July 1900; primary growth excised February 2, 1901; prompt recurrence. Beginning May 4, 1901, toxins given for about three and a half months with four weeks' rest between first and second course; *complete regression of tumor* during treatment; no further recurrence. Patient in good health for many years; died in November 1912 of what appeared to be pulmonary tuberculosis. (29, 31, 41.) 12

30. (Chapin): Mrs. B., adult; inoperable round-cell sarcoma of thoracic cavity beneath sternum; biopsy. In January 1902, toxins were given, at first every forty-eight hours; skin and subcutaneous tissue in upper part of *tumor necrosed* and there was a *profuse discharge of necrotic tissue;* during the fifth month of toxin treatment the dosage was 30 minims once weekly; *complete regression* by May 15, 1902; no harmful effects on kidneys, although chronic Bright's disease was present; no recurrence. Patient in better health than at any time prior to treatment; alive and well about four years after onset. (29, 41.) 4

31. (Coley and Boynton): H. B. M., male, aged 56; recurrent inoperable spindle-cell sarcoma of triceps muscle, deltoid region. Onset in summer of 1902; in September 1902 the tumor was excised along with some of the deltoid muscle; recurrence in February 1903. Toxins were started February 12, 1903; *regression;* no further recurrence. Patient well until death on December 25, 1928, at the age of 81, from auricular fibrillation and cerebral embolus. (29, 41, 102.) 26

32. (Coley): F. Q., male, aged 63; recurrent inoperable large spindle-cell sarcoma of cheek. Onset in January 1904; excision week after onset; prompt recurrence; second attempt at removal abandoned. Beginning March 16, 1904, toxins (Buxton VI and Parke-Davis IX) were given for three months along with a few x-ray treatments; *complete regression; cheek regained normal appearance;* no further recurrence. Patient last seen in 1910, aged 69, in good health. (29, p. 95; 73.) 6

33. (Coley): W. J., male, aged 10; inoperable thrice recurrent round-cell sarcoma of scapular region. Onset in January 1902; incomplete removal; x-ray therapy; regression; recurrence; further radiation ineffective; third operation; further x-ray therapy; third recurrence in June 1904. Beginning July 1, 1904, toxins were given for one year in the vicinity of the scars; also x-ray therapy for a time; *slow, but complete regression;* no further recurrence. Twenty years later x-ray carcinoma of left shoulder developed; repeated excisions, skin grafts, and shoulder-joint disarticulation failed

Years traced after onset

to control it. The patient died on February 4, 1952, fifty years after the onset of sarcoma; autopsy showed the presence also of bilateral bronchiolar carcinoma. (17, 17b, 18a, 19a, 20, 22, 26, 41, 73, 81.) 50

Buxton's erysipelas and prodigiosus serum, Type VII (1 case).

This preparation was made for only a short time and appeared to be less effective than the unfiltered toxins Type VI.

34. (Coley): Mrs. A. C., aged 59; inoperable thrice recurrent angiosarcoma of the breast. Date of onset not stated; 2 excisions of large ulcerated nodular growth; foul discharge; patient's general condition very poor. Beginning February 1, 1895, 51 injections of serum were given over a period of several months; also 7 doses of filtered toxins (Type V); the latter seemed less effective than the serum; *slow decrease in size; increase in mobility; improvement in general health;* remains of growth excised August 18, 1895; no further recurrence. Patient well until death in 1903 from injuries incurred in a fall downstairs; no evidence of sarcoma at that time. (13, 16, 24, 29, p. 88, 73.) 8

Parke-Davis IX (3 cases)

This was a commercial preparation of Coley toxins available from 1900 to 1907.

35. (Hundley): Mrs. A. C., aged 38; inoperable recurrent round-cell and spindle-cell sarcoma of the uterus. Onset in the fall of 1903; growth the size of a term fetal head removed by supravaginal hysterectomy in December 1903; attempt to remove cervix on January 15, 1904, abandoned because of weak heart; recurrence in right lateral fornix, springing from broad ligament, pelvic bone and fascia. January 22, 1904, toxins were started; 33 doses were given directly into the fornix and cervix; immediate decrease in size; *complete regression;* no further recurrence. Patient in good health until sudden death from severe duodenal ulcer, in July 1932. (20; 29, p. 155; 41.) 28

36. (Spencer): C. W. L., male, aged 33; inoperable spindle-cell sarcoma of entire lower abdomen, infiltrating the peritoneum, involving the rectus muscles and firmly attached to the symphysis pubis; frequent micturition; progressive weight loss. Onset in October 1905; exploratory laparotomy; biopsy specimen removed; six days later, attempt at removal made and abandoned because of extensive involvement. Beginning September 22, 1906, toxins were injected into the tumor; sharp local and general reactions; 3 courses totalling 43 doses in six months; *complete regression;* no recurrence. Patient alive and well in 1912. (12, 29, 45, 80, 99, 100.) 6½

37. (Green): J. P., male, aged 20; extensive small round-cell sarcoma of abdominal wall in the region of the umbilicus, apparently originating in the urachus; extremely adherent to omentum. Onset in early November 1906; very large calculus (3½ inches in diameter) removed from prostatic uretha in March 1906, followed by purulent cystitis; exploratory operation. Beginning January 1, 1907, 60 doses of toxins were injected into the tumor in five months, causing intense local inflammation and evident systemic reactions; *complete regression;* gain of 40 pounds. Patient alive and well in 1911. (29, 41, 55.) 5

Tracy X and XI, unfiltered (23 cases)

38. (Mudd): Miss C. N. J., aged 30; sarcoma which was primary in the left ovary and recurrent in the abdominal wall. Date of onset not stated, but it was prior to fall of 1906; curettage November 13, 1906; ovariectomy July 19, 1907; tumor 7 inches wide, almost gangrenous; rapid inoperable recurrence in abdominal wall. August 1, 1907, toxins (Tracy X) started; *complete regression;* no further recurrence. Patient alive and well in 1919. (33, 41, 108.) 12½

39. (Coley): Miss M. L. W., aged 42; recurrent leiomyosarcoma (primary in uterus)

Years traced after onset

following hysterectomy; filled lower pelvis, involved bladder wall; frequent painful micturition; general health bad. October 1, 1907, toxins (Tracy X, XI, XI F, XII & XII F) started; improvement noted in two to three weeks; *marked cessation of pain; softening; decrease in size; general health improved.* Toxins not given for eight weeks during hot weather; immediate return of symptoms, increase in size of tumor. Toxins resumed; given in low dosage with intervals of rest for nearly two and a half years, causing mild reactions; *complete regression;* no further recurrence. Patient well during the next thirty-five years; died on March 29, 1944, aged 80, from cerebral hemorrhage and hypertension. (26, 41, 73, 81, 102, 108.) 37

40. (Coley): C. B. C., male, aged 27; inoperable metastatic round-cell sarcoma, primary in muscles of lower lumbar region; metastasis involving entire thickness of lower jaw. Onset in September 1907; primary tumor became size of man's two fists in few weeks; excision; unhealed wound 6 x 8 inches; patient generally emaciated, unable to walk unaided. Beginning November 19, 1907, toxins (Tracy X) injected into gluteal muscles; also 5 doses of filtrate (Tracy X F) injected into tumor of jaw; slow decrease in size; marked increase in mobility; general health improved; gain in weight. Toxins were given for eight months; improvement more rapid after first six weeks; *complete regression;* no further metastasis. Patient in good health and very active for thirty-seven years; in the autumn of 1944, a carcinoma developed at the site of the original growth in the lumbar region, causing death on June 11, 1946 at the age of 73; no toxins were given for this neoplasm. (22, 24, 29, 73, 80, 81.) 39

41. (Howe): Mrs. C. McM., aged 50; recurrent inoperable round-cell sarcoma of the uterus; infiltrating mass filled pelvis; clinically resembled carcinoma; severe, pain and bladder symptoms; general health bad; prognosis hopeless. Date of onset not stated. Beginning April 7, 1908 toxins four times weekly; *general condition improved; pain ceased; tumor decreased steadily in size.* Toxins stopped during hot weather; severe pains immediately returned; toxins resumed and given steadily, 119 doses in twenty-six months; *complete regression;* no further recurrence. Patient in good health until death, at the age of 81, from cerebral arteriosclerosis. (10, 25, 29, 41.) 28

42. (Reshower): Mrs. S. R., adult; extensive recurrent round-cell sarcoma involving all abdominal viscera. Date of onset not stated; primary growth removed from pelvis as well as possible, but all organs were involved in the adhesions; fistula remained; x-ray treatment given briefly; stopped because it caused so much dermatitis; recurrent tumor filled whole abdomen; prognosis grave. Beginning July 7, 1908, toxins given aggressively for nine months; *complete regression;* no further recurrence. Patient alive and in excellent health in 1915. (41, 81.) 7

43. (Tosier): Female, aged 22; inoperable spindle-cell sarcoma of left ovary, involving the broad ligament, uterus and intestine. Onset in October 1907; exploratory laparotomy in December 1908; due to extensive involvement and fear of hemorrhage, only biopsy was performed; prognosis hopeless. Toxins begun after her return home; given daily at first; *immediate improvement; gain of 60 pounds.* Toxins given for ten months; periods regular; no recurrence; had second child in autumn of 1909, year after toxins stopped. Patient was in good health in 1912. (26, 29, 41, 58, 108b.) 5

44. (Leach): H. H., male, aged 33; twice recurrent inoperable spindle-cell sarcoma of the right kidney; metastases involved intestines extensively. Date of onset not stated. Patient had been ill for six months; lost 40 pounds, coughed; chest films revealed only "bronchial trouble," thought to be tuberculosis. Exploratory laparotomy on May 30, 1908; practically solid growth weighing 13½ pounds and filling whole abdominal cavity removed; recurrent tumor size of orange; on April 17, 1910, whole omentum removed up to stomach; metastases on right side, involving intestines; exploratory incision; condition inoperable. July 1, 1910, toxins started; 41 doses in sixty days; *complete regression; patient regained 40 pounds and former strength;* perfectly well in 1916. (41, 42, 81.) 6

Years traced after onset

45. (Da Costa): Female adult; huge inoperable spindle-cell sarcoma of thigh and groin. Date of onset not stated. Portion of growth removed surgically in 1910; toxins begun immediately thereafter; given daily; violent reactions every day for weeks; *complete regression;* no recurrence after four years. (45a.) 4

46. (Haines): J. M., male, aged 52; inoperable round-cell sarcoma of right rectus and internal oblique muscles; tumor size of hen's egg; immovable. Onset prior to April 1910; exploratory operation; incomplete removal, April 25, 1910; two days later, toxins begun; 3 courses in six months; *considerable sloughing of necrotic tumor tissue; complete regression.* Patient well and free from recurrence until death from heart attack in 1933. (29, p. 166; 41, 81, 81a.) 22

47. (Harmer): L. E. F., female, aged 46; extensive recurrent infiltrating spindle-cell sarcoma of antrum and ethmoid. Onset in 1904; had 6 operations; recurrences. Beginning February 19, 1912, toxins given for six weeks after sixth (incomplete) operation; *remains of growth apparently destroyed;* no further recurrence. Patient in excellent health next twenty years; died from cerebral hemorrhage on April 16, 1932. (58, 59, 72, 81.) 28

48. (Coley): J. C. K., male, aged 52; inoperable spindle-cell sarcoma of retroperitoneal region and iliac fossa. Onset in December 1911. Toxins given for four weeks, beginning March 26, 1912; decrease in size of tumor; softening; incision; necrotic tissue evacuated. Toxins resumed; given several weeks longer; *complete regression;* no recurrence. Patient alive and well in 1918. (29, 31, 42.) 6

49. (Stewart): D. A. D., male, aged 56; mixed-cell sarcoma of right groin, "decidedly malignant"; loss of strength and appetite; 15-pound weight loss. Onset, February 1912; inoperable. Toxins begun in April 1912; meticulously administered; *complete regression;* no recurrence. Patient remained in excellent health more than twenty years; then carcinoma of stomach developed; metastases to spine; death on September 21, 1934, aged 77, from general carcinomatosis, chronic myocarditis and arteriosclerosis. (41, 72a, 102.) 22

50. (McDonald and Burns): M. P., female, aged 27; inoperable round-cell sarcoma of the kidney, involving the retroperitoneal glands. Onset early in 1912; surgical exploration revealed an inoperable condition; there was a large retroperitoneal mass as well as a mass occupying the lower pole of the kidney; no attempt at removal; condition hopeless in September 1912 when toxins, (Tracy XI) were started; given intramuscularly into buttocks; febrile reactions to 105°F.; *immediate improvement; sinuses healed; complete regression.* Patient gained 20 pounds; well. Multiple fibroids developed, requiring panhysterectomy in 1927; no evidence of disease at site of former sarcoma or elsewhere. She subsequently had several operations for intestinal obstruction due to adhesions; no evidence of malignant disease. Patient alive in 1958, forty-six years after onset. (29, 40, 41, 42, 77, 80, 108.) 46

51. (Shields): Mrs. F. H. D., aged 48; inoperable myxosarcoma of left tonsil and palate; submaxillary glands enlarged; tumor the size of a hazel nut beneath left ear. Onset in the spring of 1913. Biopsy of buccal tumor. September 29, 1913 toxins started —at first daily, then every forty-eight hours, some injected into tumor; dose increased to 21 minims; *complete regression; patient gained 16 pounds;* in excellent health; no recurrence. Sudden death from pneumonia, following influenza in 1918. (31, 41, 94a.) 5

52. (Cruikshank): W. L. W., male, aged 28; large spindle-cell sarcoma of retroperitoneal glands. Onset about October 1913; exploratory operation; three months later, colostomy necessary because of complete obstruction; mass extended to umbilicus; prognosis was probable death in two to three weeks. Beginning February 4, 1914, toxins injected into abdominal muscles; (no reactions from Parke-Davis XII given first five days; thereafter Tracy XI given; caused marked local and general reactions); total of 87 doses in five months; *complete regression;* no recurrence. (Subsequently this man's wife had 5 children in twelve years.) He remained in good health

Years traced after onset

except for gallstones in 1942 (operation), coronary thrombosis in 1949, and a slight cerebral hemorrhage in 1956 with complete recovery. He was apparently in excellent health in 1958. (31, 41, 81.) 44½

53. (Coley): J. K., male, aged 31; inoperable round-cell sarcoma of the nasopharynx and right superior maxilla, involving the ethmoid and frontal bones. Onset in April 1913; neuralgic pain at sites of involvement and also in temporal and supraorbital regions; right naris occluded; weight loss; biopsy. Beginning April 22, 1914, toxins injected intramuscularly into right chest for four months; *almost immediate diminution in size of tumor; complete regression in four months;* no recurrence. Patient alive and well in 1924. (1c, 41, 73.) 10

54. (Coley and Zacharie): Mrs. D. B., aged 22; extensive inoperable fibromyxosarcoma of calf, thigh and hip; possible lymphadenopathy. Onset November 1913; larger mass measured 28 inches by 17 inches; smaller tumors also present, filling popliteal space; 50-pound weight loss; general health poor; severe pain; biopsy. Toxins (Tracy XI & Tracy XI F) started May 18, 1914; at first injected into buttocks; later into growths on hip or surrounding tissues; *some decrease in size of tumors; increase in mobility; atrophic changes; no necrosis, sloughing or discharge; very little absorption; apparently toxins destroyed malignant elements without affecting fibrous stroma.* Patient regained strength and weight very slowly; alive and well, except for some hypertension, in 1959. (41, 73, 81.) 45½

55. (Williams): Mrs. R. A. H., aged 56; inoperable recurrent sarcoma of nares and superior maxilla. Onset in autumn of 1913; nose cauterized; primary growth removed; recurrence; extensive second operation on left superior maxilla; left lower orbital plate removed; recurrence; condition believed hopeless. Beginning September 1, 1914, toxins given daily; 62 intramuscular injections in six and a half months (only 7 marked reactions); *tumor disappeared* in three months. Patient in good health for five years; then epithelioma of hard palate developed; 3 radium treatments in 1920; disease not controlled; later extended to left naris and antrum; further palliative radiation in March 1921 and March 1922 (no toxins); death on March 9, 1923. (29a, 41, 81.) 9

56. (Tuholske): M. B., male, aged 28; round-cell sarcoma of right pharynx and nasopharynx; almost complete obstruction of air. Date of onset not stated. Biopsy; toxins started in May 1915; no effect from massive doses of Parke-Davis XII given intramuscularly, remote from tumor; first dose of Tracy XI caused violent reactions, chills, high fever and necrosis in center of tumor; *complete regression in six weeks.* Patient left hospital feeling well; a few months later, recurrence on the opposite side of the pharynx, and abducens nerve paralysis (metastasis in region of hypothalamus). Daily intramuscular injections of toxins into arms for one week; no reactions or effect on tumor; then injections given in thighs and abdominal wall alternately; marked febrile reactions, causing *rapid complete regression of tumor*, though not of nerve paralysis. Toxins stopped in the last week of January 1916; patient began to vomit; very drowsy; in coma for three and a half weeks; weight fell to 89 pounds; then began to improve, and gained 28 pounds in seven weeks; *complete regression of cerebral metastasis; speech and sight normal; nerve paralysis subsided;* however, symptoms of eunuchism apparent when he recovered from coma; no further recurrence or metastases; in good health. Mild hypertension developed in 1942; slight hemiplegia, 1945; moderate arteriosclerosis, 1946; died from coronary occlusion and arteriosclerotic heart disease, November 23, 1948 at the age of 63. (Detailed history deserves study; see ref. 80, case 23.) (41, 42, 80, 81.) 33

57. (Follansbee): Mrs. D. M. W., aged 23; recurrent small round-cell sarcoma of the gluteus maximus muscle. Onset in February 1915; motion of hip joint steadily diminished; tumor grew slowly until after birth of child, October 10, 1915; loss of 35 pounds; severe pain; surgical removal (tumor weighed 24 ounces); prompt recur-

Years traced after onset

rence, size of hen's egg. February 2, 1916, toxins (Tracy X and XI) started; first dose into tumor, later into region of growth; *complete regression in three weeks.* Toxins stopped for one week; prompt recurrence on inner thigh (adductor muscles); toxins resumed; given into tumor daily; tumor grew to size of grapefruit, *then broke down and discharged necrotic tumor tissue; disappeared completely* during toxin therapy given for eight months. Patient had 4 more children; in 1956 ulcerative colitis developed with peritonitis; operated on; seriously ill, but recovered; alive and free from any evidence of recurrence in October 1958. (Detailed history deserves study; see ref. 80, case 24.) (41, 73, 80, 81.) 43½

58. (Donaldson): Female, aged about 20; recurrent inoperable sarcoma of scalp. Date of onset not stated. Primary tumor excised; local recurrence. In 1918 treated with toxins for over four months; shortly after first febrile reaction, tumor began to shrink; in one month, *complete regression;* no further recurrence. Patient alive and well in 1928. (81.) 10

59. (MacLean): Male, aged 2; recurrent rapidly growing angiosarcoma of right cheek; date of onset not stated. Primary growth excised; prompt recurrence. In 1918 treated with toxins for two and a half months; injected directly into tumor; little febrile reaction; *complete regression;* no further recurrence. Patient alive and well 1943. (81.) 25

60. (Calkins): Mrs. M. M., aged 26; inoperable mixed-cell sarcoma of ovary; extensive involvement of intestines and pelvis; onset in September 1919; exploratory operation January 29, 1920; found large degenerated left ovary, large cauliflower masses between the tumor, cecum, sigmoid flexure and rectum, and an appendix the size of a large cucumber; performed bilateral salpingo-oophorectomy, panhysterectomy and appendectomy; impossible to remove areas of involved intestine. Toxins begun one week after operation; given steadily for twelve months; *complete regression of metastatic growths;* no further recurrence or metastases. Patient alive and in excellent health in 1927. (5, 41, 42, 81.) 7

Parke-Davis XII and XIII (10 cases)

These commercial preparations of Coley's toxins were available from early 1907 to 1950. See references 77 and 80 regarding the comparative weakness of these products.

61. (Pilcher): Male, aged 55: inoperable round-cell sarcoma of abdominal wall. Date of onset not stated; exploratory operation; specimen removed. Beginning in August 1908, toxins were given for four months; *gradual complete disappearance; gain of 20 pounds.* Patient well and free from recurrence in 1914. (29, p. 165; 41.) 6

62. (Ochsner): Mrs. V. H., aged 17; inoperable small round-cell sarcoma of axilla. Onset in February 1910; extensive operation March 11, 1910; mass the size of a grapefruit excised, but involved areas could not be completely removed, as axillary nerves and vessels were surrounded. March 26, 1910, toxins were started; injected into deltoid; febrile reactions, 102°–105°F.; given six months; *remains of growth regressed completely;* no recurrence. Patient married and had 3 children; was alive and in excellent health in 1946. (81.) 36

63. (Pollak): P. H., female, aged 22 months; inoperable angiosarcoma of mediastinum, causing severe pressure erosion of spine and ribs, and paralysis of both legs. Onset at age of 5 months, in December 1922; child suddenly stopped walking at 21 months; total inability to stand due to paresis of both legs; mass between scapula and spine; anemia; Dr. Lilienthal conducted surgical exploration on April 15, 1924; condition inoperable, but he removed part of tumor for biopsy. Beginning April 25, 1924, toxins injected into gluteal muscle daily for eleven days; marked febrile reactions (to 106°F.); extraordinarily rapid wound healing; anemia became temporarily worse, then blood picture rapidly improved; child began walking three weeks after

Years traced after onset

first injection of toxin; in next few months pertussis, measles and bronchitis developed, all severe; *complete regression of tumor;* the resected ribs regenerated; the child developed and grew normally. Later, she married and had 2 normal children; she was alive and well in 1959. (53, 67, 76, 80 (case 28), 81.) 37

64. (Blum): Mrs. E. A., aged 37; malignant myoma weighing 15 pounds, removed surgically. Onset in 1923; x-ray examination indicated extensive metastases to femur, sacrum and skull; anemia, poor general condition. July 21, 1927, toxins started in large doses; *complete recovery.* Patient gained weight and strength; no recurrence or further evidence of skeletal metastases; alive and well in 1933. (6, 35a, 41, 67, 76.) 10

65. (Crawford): L. V. McN., male, aged 26; recurrent reticulum-cell sarcoma, primary in bicipital region, with metastases in axilla and abdominal wall. Onset in November 1927; primary growth excised in February 1928; recurrence under left arm one month later; biopsy; one x-ray treatment on May 29, 1928; toxins then begun, and given with intervals of rest for five years; *at first further metastatic nodules appeared but they regressed under continued treatment;* no further metastases after autumn 1931. Patient in excellent health except for appendectomy in 1952; alive and well in 1958. (41, 81.) 31

66. (Fowler): C. S., female, aged 21; inoperable neurofibrosarcoma of popliteal space. Onset in February 1929; exploratory operation May 14, 1929; excision of tumor impossible because of involvement of vessels and nerves; 2 specimens removed. May 26, 1929, toxins begun; tumor disappeared in five to six weeks; evidence of recurrence; toxins resumed; given with intervals of rest for six years; *complete regression;* no further recurrence. Patient married and was said to have had a child; alive and well in 1945. (81.) 16

67. (Burke): H. R., female, aged 19; terminal sarcoma of neck, face, submaxillary region involving bones, subcutaneous tissues, especially the forehead, parietal regions, left cheek, and jaw. Onset in March 1931; hard nodular mass in neck below angle of right jaw; incision; x-ray therapy produced no relief; tracheotomy for edema of glottis; radium given, without benefit; bilateral chronic mastoid developed; operation on January 28, 1932; radium again; marked exophthalmos of both eyes; morphine required. Beginning June 12, 1932, toxins intramuscularly *caused improvement,* but were stopped because of painful indurations; recurrence; x-ray therapy; recent recurrent nodules disappeared, leaving masses in right submaxillary and submental regions; extensive mass in floor of mouth; 2 more courses of toxins intravenously; marked reactions; *all tumor masses disappeared;* part of tongue sloughed; *complete recovery.* Patient married and had children; was alive and well in 1958. (41, 81.) 27

68. (Coley): N. P., female, aged 26; inoperable retroperitoneal sarcoma, unclassified; firm mass filled whole left lower abdomen and pelvis; clinically regarded as neuroblastoma, myosarcoma or liposarcoma. Onset in 1928; needle biopsy; traction to leg; local applications; diathermy, physiotherapy; *recovered full use of limb; well for five years.* Pain recurred; exploratory operation; pain increased; large bulging mass (27 cm. in diameter) arising from pelvis extending almost to mid-axillary line in flank filling lower right quadrant to umbilicus; x-ray examination showed that the upper anterior half of the right ilium was involved, apparently from external pressure erosion; x-ray therapy; apparent complete regression in three months. Beginning June 3, 1935, 20 injections of toxins were given in twenty-eight days; the first 11 were given intramuscularly, the next 7 intravenously, and the last 2 intramuscularly; there were febrile reactions to 105°F. *Patient gained weight, and general condition improved.* She was married in the autumn of 1935; artificial menopause (radiation-induced) in 1936; menstruation occurred again on March 6, 1937; periods regular after August 1937; had 2 normal pregnancies and confinements in 1939 and 1940; no recurrence or metastases; alive and well in 1957. (81.) 29

Years traced after onset

69. (Dodd): Mrs. Y., aged 52; extensive recurrent inoperable desmoid sarcoma of left erector spinae muscle. Onset prior to March 1936; primary growth excised April 30, 1936; postoperative x-ray therapy during next eighteen months did not prevent recurrence in October 1936, nor control it; another excision attempted in November 1937; skin, scapula, rib and pleura fused into homogeneous mass of tumor tissue; biopsy; operation abandoned; further deep x-ray therapy proved ineffective; condition hopeless; huge lumpy mass. Beginning April 2, 1938, toxins were injected into shoulder muscles; continued weekly for eight months; marked reactions; *complete regression* by absorption and saneous discharge in twenty months; second course of toxins begun January 29, 1940; given every other week alternating with T.A.B. vaccine to relieve causalgic pains; *complete resolution of scar tissue;* continued seven months; no further pain after August 1940. Patient alive and well in 1957. (Treated as out-patient, as she had 4 children and could not afford hospitalization.) (81.) 21

70. (Hasley): Male, aged 53; generalized hemangioendotheliomata (site of primary unknown), with lesions on hands, arms, face, head, body and legs. Onset in December 1946. Some lesions bled and were painful; telangiectasia under tongue, but no bleeding from mucous membranes. Penicillin, rutin and x-ray therapy (to 3 lesions on face) tried without benefit; March 24, 1947, surgical removal of a few tumors on the abdomen and head, some by scalpel, other by electro-desiccation; aspiration biopsy of tumor on left arm; x-ray treatment (1200 to 1800 r) for a few lesions without apparent benefit. Beginning April 1, 1947, toxins were injected intravenously, 12 doses in eighteen days; febrile reactions averaged 102–104°F.; *within five days the tumors were "quite dry and falling off, with considerably less bleeding of the irritated lesions";* marked regression in eight weeks; *complete regression* of all tumors; little atrophy and no telangiectasis; no evidence of disease. The patient was well for eleven years; in the spring of 1958 a malignant melanoma developed on the right shoulder; excisional biopsy on June 13, 1958. Patient well, with no further evidence of disease in July 1958; metastasis in cervical region few months later; receiving toxin therapy (Johnston XV), spring 1959. (81.) 12½

Comment: It is of interest that only 9 patients in this successful series received radiation therapy.

It was thought wise to analyze the preceding 70 cases to see if certain factors in the patient or in the treatment could account for the successful results. The classification with respect to operability or inoperability was made by the surgeon when the case was treated. This designation undoubtedly varied at least to some degree with the surgeon, and therefore the distinction is not too exact since no precise criteria are available for the differentiation. "Primary inoperable tumor" refers to inoperability at the time when toxin therapy was first considered, and "recurrent inoperable tumor" refers to inoperability after recurrence had taken place.

Analysis of Series A

Stage of disease when toxins begun

Primary inoperable (31 cases):

*1, 3, 4, 8, 11, 14, 15, 18, 20, 25, 27, 28, 30, 36, 37, 45, 46, 47, 48, 51, 52, 53, 54, 55, 56, 60, 61, 62, 63, 66 and 67.

Recurrent inoperable (32 cases):

six times (1 case, *47);

three times (5 cases, ⁂6, 9, 22, 33 and 34);
twice (5 cases, ⁂2, 10, 16, 23 and 44);
once (21 cases, ⁂1, 7, 12, 13, 17, 19, 21, 23, 29, 31, 35, 38, 39, 41, 42, 57, 58, 59 and 69).

Metastases present (8 cases):
⁂16, 20, 40, 44, 60, 64, 65 and 70.

Cachexia present or general condition poor (20 cases):
⁂1, 3, 4, 5, 7, 13, 23, 34, 39, 40, 41, 44, 48, 50, 52, 53, 54, 57, 63 and 67.

Concurrent complications (2 cases):
Pregnancy (⁎ 12, normal confinement);
Bright's disease (⁎ 30, no ill effects).

Radiation treatment prior to toxins (7 cases)

⁂33—several courses of x-ray therapy; died from x-ray cancer fifty years later.
⁂42—brief course x-ray therapy caused severe dermatitis.
⁂65—1 x-ray treatment.
⁂67—radium and x-ray therapy (large amount) did not control disease.
⁂68—x-ray therapy (8,500 r) was followed by complete regression of the tumor.
⁂69—x-ray therapy did not prevent or control recurrence.
⁂70—x-ray therapy (small amount) did not control disease.

Surgery prior to toxins (54 cases)

Biopsy and/or exploration (32 cases):
⁂1, 3, 4, 5, 8, 11, 14, 15, 17, 18, 20, 25, 27, 28, 30, 32, 36, 37, 43, 44, 49, 50, 51, 52, 53, 54, 56, 61, 63, 66, 68 and 70.

Incomplete removal (12 cases):
⁂6, 19, 23, 24, 26, 33, 40, 45, 46, 47, 60 and 62.

More than 1 operation (17 cases):
⁂2, 5, 6, 7, 9, 10, 16, 19, 22, 23, 24, 32, 33, 34, 35, 47 and 69.

Untreated (22 cases)

Primary inoperable: 1 case (⁂48).

Recurrent or metastatic (primary tumor removed) (21 cases):
⁂7, 12, 13, 16, 21, 22, 23, 26, 31, 34, 35, 38, 39, 41, 42, 55, 57, 58, 59, 64 and 65.

Treatment during toxin therapy (9 cases)

Radiation (2 cases):
⁂32—a few x-ray treatments.
⁂33—x-ray therapy, mostly given prior to toxins.

Evacuation of necrotic tumor tissue (5 cases):
⁂8, 15, 17, 30 and 48.

Treatment after toxin therapy (13 cases)

Radiation (2 cases):
X-ray treatments (136 in twenty-eight months) finally controlled disease; x-ray cancer developed some years later; excised—1 case (⁂28).

X-ray treatment caused some regression, although both x-ray and radium therapy prior to toxins produced no apparent benefit—1 case (# 67).

Surgery (6 cases):

Remains of growth excised—1 case (# 54).

Scar tissue or fibrous stroma excised—3 cases (# 10, 13 and 22).

Amputation—1 case (# 6).

Plastic operation—1 case (# 9).

Immediate and final effects of toxin therapy on malignant lesions

Recurrence or metastases developed during or shortly after toxin therapy; complete regression with further toxin therapy (10 cases):

6, 14, 23, 39, 41, 56, 57, 65, 66 and 67.

Tumor continued to regress after toxins stopped (7 cases):

1, 3, 5, 7, 56, 63 and 64.

Malignancy destroyed: fibrous stroma remained (2 cases):

7 and 54.

Complete regression apparently due to toxins; traced five to sixty-two years: (65 cases).

Complete regression apparently due to toxins; traced four years: (3 cases):

8, 30, 45.

Complete regression and control of disease due more to radiation than to toxins (2 cases):

28 and 68

Development of other forms of cancer five to fifty years later (10 cases)

Hepatoma, twenty-four years after onset of sarcoma—1 case (# 27).

X-ray cancer (basal-cell epithelioma) twenty years after onset of sarcoma; repeated surgery, finally disarticulation of shoulder; death fifty years after onset of sarcoma; autopsy showed also a bronchiogenic carcinoma—1 case (# 33).

Carcinoma in lumbar region at site of former sarcoma, thirty-seven years later—1 case (# 40).

Carcinoma of stomach, twenty years later—1 case (# 49).

Epithelioma of hard palate, five years after sarcoma of naris; not controlled by radium; death nine years after onset of sarcoma—1 case (# 55).

(*Note*: The foregoing 5 patients died from their second neoplasm; the following did not.)

Epithelioma of neck, fifty-nine years after onset of sarcoma—1 case (# 2).

Basal-cell epithelioma of nose, forty-five years later—1 case (# 15).

X-ray carcinoma of abdominal wall, multiple, about eight years after onset of sarcoma—1 case (# 28).

Multiple uterine fibroids fifteen years after onset of sarcoma of kidney; panhysterectomy; alive forty-six years after onset of sarcoma—1 case (# 50).

Malignant melanoma eleven years after onset; hemangioendotheliomata; excisional biopsy; patient now receiving toxins for metastases—1 case (# 70).

Conditions other than cancer, causing death five to forty-seven and a half years after onset of sarcoma (19 cases)

Pneumonia; influenza—1 case (# 51).
Bronchopneumonia (also arteriosclerosis)—1 case (# 15).
Pulmonary tuberculosis—1 case (# 29).
Herpes, involving Gasserian ganglion—1 case (# 26).
Hemorrhage due to gastric or duodenal ulcer—2 cases (# 24 and 35).
"Unrelated causes"—1 case (# 23).
Cardiovascular diseases—12 cases (# 1, 2, 3, 7, 15, 31, 39, 41, 46, 47, 49 and 56).

Patient alive but not well, eleven to forty-six years after onset of sarcoma (4 cases)

Senile debility, forty-six years later—1 case (# 50).
Hypertension, forty-three years later—1 case (# 54).
Ulcerative colitis, forty-five years later—1 case (# 57).
Malignant melanoma, eleven years later—1 case (# 70).

Patient alive and in good health when last traced, four to sixty-two years after onset of sarcoma (42 cases)

Cases 4–6, 8–14, 16–22, 25, 28, 30, 32, 36–38, 42–45, 48, 52, 53, 58–69.

SERIES B

35 CASES OF OPERABLE SARCOMA SUCCESSFULLY TREATED BY TOXIN THERAPY

The following 35 patients are the only ones known to us with operable sarcoma of the soft tissues (other than lymphosarcoma) successfully treated by Coley toxins before or after operation, in which the diagnosis was confirmed microscopically. The first 17 cases listed were primary operable tumors; the last 18 were recurrent operable tumors. In Cases # 3, 10, 14, 16 and 17 a small amount of radiation therapy was also given; in Case # 31, somewhat more. In Case # 12, concurrent pregnancy was a complication. In Case # 16, three other types of neoplasm (endometrial polyps, cystic adenoma and basal-cell carcinoma of the face) developed, seventeen, nineteen and twenty-seven years after the onset of sarcoma. In Cases #1, 23, 30 and 33 other types of neoplasm also developed, fifty-seven, fifteen, twenty-seven and twenty-two years respectively after onset of sarcoma—1 basal-cell carcinoma of the face, 1 carcinoma of the prostate, and 2 carcinomas of the stomach. Patients # 18, 27, 28 and 33 were the only ones with recurrent operable sarcoma of the soft tissues treated with toxin therapy alone and no further surgery, that remained well. (In Case # 10 among the Operable Failures in Series D, recurrent, (to be published later) the tumor also regressed completely, but recurred.)

Primary tumors (17 cases)

1. (Davies): Mrs. O. C. S. D., aged 35; fibrosarcoma of abdominal wall, 4 inches long. Onset in August 1900; surgical removal September 15, 1900; two weeks later

Years traced after onset

toxins begun (Buxton VI); given for six weeks in vicinity of cicatrix; no recurrence. Patient in good health next fifty-seven years; basal-cell carcinoma on cheek excised September 13, 1957; coxa vara developed; patient became bedridden; alive at the age of 92, in 1958. (41, 81.) 57½

2. (Coley): L. I., female, aged 19; sarcoma of groin. Date of onset not recorded; surgical removal on June 20, 1907. Beginning July 23, 1907, toxins (Buxton VI) begun; 18 injections in thirty-two days; no recurrence. Patient alive and well in 1915. (41, 73.) 8

3. (Lunding-Smith): Male, aged 10; extensive synovioma of popliteal space, involving capsule of knee joint. Date of onset not recorded; surgical removal in 1909. Prolonged course of toxins (Tracy XI) after operation; also a few x-ray treatments; no recurrence. Patient alive and well in 1913. (29, 42.) 5

4. (Coley): V. T., male, aged 39; myxosarcoma of left scapular region. Onset in September 1909; surgical removal; toxins (Tracy XI) after operation for three months in region of former growth, at first daily; no recurrence. Patient in excellent health for next thirty-four years, until late 1943. He died on July 24, 1944, at the age of 75, from uremia "due to hypertrophy of the prostate." (29, 41, 81.) 35½

5. (Harmer): L. A. W., male, aged 55; extensive small round-cell sarcoma of antrum and ethmoid, infiltrating in all directions; whole naso-antral wall destroyed. Onset in July 1910; two operations, October 14 and November 28, 1910. Toxins (Tracy XI) begun December 5, 1910; 49 injections in five and a half months; reactions often severe; no recurrence. Patient in good health December 12, 1911; not traced after 1915. (No record of death found in next thirty-five years, Massachusetts.) (58, 59.) 5

6. (Coley and Fisher): B. C. C., male, aged 7; fibrosarcoma of nerve sheaths involving pectineal muscle and glands of groin; rapid growth. Onset in November 1910; surgical removal December 4, 1910; possible recurrence in inguinal region. Beginning December 29, 1910, toxins (Tracy XI and Parke-Davis XII) given for three months; gain in weight during treatment; no recurrence; normal development. Patient became a physician; was alive and well in 1958. (29, 81, 108.) 48

7. (Haines): Mrs. R., aged 26; round-cell sarcoma of breast. Onset in January 1911. Surgical removal of breast, pectoral muscles and gland-bearing fat in axilla; June 1911, after operation, toxins (Tracy XI) for one year; weight gain of 50 pounds; no recurrence. Patient well when last seen in 1929. Died of unknown cause, about 1933. (41.) 22

8. (Reilly): H. C. S., male, aged 34; small-cell sarcoma of head of colon. Onset in 1915; at operation, 18 inches of ileum and cecum resected. Toxins (Tracy XI) given postoperatively (duration not recorded); no recurrence. Patient died on April 1, 1950, from coronary embolism, at the age of 70. (2, 41, 81.) 35

9. (Calkins): Mrs. O. L., aged 28; extensive sarcoma nearly filling pelvis, involving upper portion of vagina. Onset in May 1914, eleven months after abdominal hysterectomy for "large rapidly growing uterine fibroid"; sarcoma completely removed surgically via vagina and lower median incision. Beginning January 1, 1915, toxins (Tracy XI) given for nine months; no recurrence. Patient alive and well in 1933. (42.) 19

10. (Coley): J. R., male, aged 35; fibrosarcoma of thigh, size of grapefruit. Onset in May 1920; hip-joint amputation advised by Mayos, Deaver, and Bloodgood; Coley advised exploration and removal if possible, followed by toxins; this was carried out on June 21. Toxins (Tracy XI) given for six months postoperatively; also 5 x-ray treatments. Patient gained 66 pounds; no recurrence; alive and well in 1958. (41, 73, 81.) 38

11. (Ward): W. W., male, aged 42; mixed-cell sarcoma of leg in region of calf. Onset in October 1909; surgical removal September 4, 1910; toxins (Parke-Davis XII) postoperatively; 65 injections in eight months with interval of six weeks' rest;

Years traced after onset

no recurrence. Patient remained healthy until death from acute cardiac failure at the age of 80, on February 14, 1949. (2, 81, 109b.) 39

12. (Coley and Levine): Mrs. B. K., aged 34; neurogenic sarcoma of deltoid region of right arm, size of small orange. Onset in December 1918. First operation in June 1920. Toxins (Parke-Davis XIII) given postoperatively beginning June 19, 1920; 75 injections in ninety days, all into the pectoral muscles except 3 into the outer limits of the tumor area; recurrence. Second operation in February 1921; patient 3 months' pregnant; second recurrence (grew faster after confinement); pain in both axillae. Toxins continued one year; radium inserted into tumor (7,900 mch.) during toxin therapy; another slight recurrence. Toxins resumed; given more aggressively, causing marked reactions; total duration three and a half years; no further recurrence. Patient returned to active work running a bookstore; fractured right arm at site of former growth, on November 20, 1948; bone healed normally. She was in excellent health in 1958. (41, 73, 81.) 39

13. (Coley): Mrs. J. M., aged 44; fibrosarcoma in right groin, size of small egg. Onset in April 1922; radium administered (no details given); surgical removal of tumor on October 3, 1922. Toxins (Parke-Davis XIII) given for several weeks; complete recovery, no recurrence. Patient alive in 1958, at the age of 80 years. Had gastric ulcer in 1928; hypertension; and cerebral hemorrhage in 1955. (41, 81.) 36

14. (Lilienthal): L. F. B., male, aged 44; spindle-cell sarcoma of lower chest wall. Date of onset not recorded; 1 x-ray treatment (erythema dose); surgical removal. Toxins (Parke-Davis XIII) given for six weeks postoperatively, beginning June 10, 1924; no recurrence; lipoma developed in 1936; excised; recurred two years later; again removed. Patient had arteriosclerosis in later years and died suddenly from a heart attack on March 20, 1951. (81.) 27

15. (Crawford): J. P. C., male, aged 60; myxosarcoma posterior to tibia, anterior to muscles and calf of leg, size of hen's egg. Onset in November 1926; surgical removal on December 29, 1926. Toxins begun on eighth postoperative day; 19 injections in thirty-four days; no recurrence. Patient alive and well in 1945; died from cerebral hemorrhage on February 9, 1951. (81.) 24

16. (McCreery): M. A. J., female, aged 30; mixed spindle-cell and giant-cell sarcoma of thigh. Onset in May 1927; biopsy, June 20; surgical removal, June 27, 1927. Severe staphylococcus infection for nine days; 1 radium pack treatment; severe skin reaction. Toxins (Parke-Davis XIII) begun; in sixty days received 16 intramuscular injections; recurrence in November 1927; wide excision; more toxins intravenously for six weeks; (patient was interning at Bellevue during her illness); no further recurrence. Radiation menopause in 1944 for menorrhagia due to endometrial polyps; thyroidectomy in 1946 for cystic adenoma; small basal-cell carcinoma excised from forehead in 1954. Patient in excellent health in 1959. (81.) 32

17. (Coley): O. C., female, aged 10½; neurogenic sarcoma of fascia lata. Onset in October 1933; surgical removal November 11, 1933; 3 radium pack treatments (15,000 mch.). Toxins begun the day before first radium treatment; injections given for nearly two years. Acute appendicitis in September 1935; given anti-peritonitis serum, causing severe serum shock. Married in 1949; 2 children; no recurrence; alive and well in 1956. (41, 81.) 23

Recurrent tumors (18 cases)

18. (Coley): Mrs. D. L., aged 40; thrice recurrent sarcoma of cheek. Onset in June 1897; excision; prompt recurrence; second operation; recurrence. Toxins (Buxton VI) given for third recurrence; complete regression; no further recurrence. Patient alive and well in autumn of 1917; not traced thereafter. (16e, 29, 73, 81.) 20

19. (Coley): Male, aged 6; thrice recurrent spindle-cell sarcoma of palm of hand,

Years traced after onset

with axillary metastasis. Onset in 1898; excision, then amputation of ring and little fingers and metacarpals; recurrence quickly followed each operation; in the autumn of 1899, an axillary metastasis developed and was removed. Toxins (Buxton VI) then given for three months; no further recurrence or metastasis by 1901. (16f.) 3

20. (Matagne): Female (?), aged 36; sarcoma of left breast. Date of onset not stated. Removed surgically in 1907; rapid recurrence. Toxins given locally prior to second operation; no further recurrence. Patient well and free from disease in 1913. (71g.) 6

21. (Coley): Miss K., aged 22; four times recurrent sarcoma of breast. Date of onset not recorded. Four operations by Kammerer had been followed each time by rapidly growing recurrent tumors. Toxins (Tracy XI) started in July 1906, for treatment of fourth recurrence; 2 small masses then excised; a final small recurrent tumor also removed; toxins continued by family physician; no further recurrences. Patient well in 1931. (29, 42.) 25

22. (Coley): E. M. A., male, aged 46; recurrent mixed-cell sarcoma of triceps muscle. Onset in September 1907; excision in October 1907; prompt recurrence; second surgical removal in November 1907. Beginning December 10, 1907, toxins (Tracy XI) for three weeks; did not prevent second recurrence. Larger doses of toxins, some into tumor, caused marked regression and softening; necrotic tumor evacuated; toxins resumed for three weeks; another recurrence; not controlled; disarticulation of shoulder joint; no further recurrence. Patient died from chronic nephritis and uremia on June 21, 1913. (2, 41, 42, 73, 110b.) 6

23. (Green): J. McG., male, aged 31; recurrent ulcerated myxosarcoma of dorsal surface of right wrist, involving ulna. Onset in January 1907; enucleation, December 15, 1907; prompt recurrence, ulceration. Beginning July 21, 1907, toxins (Tracy XI) injected daily into tumor for a week; no effect; amputation at elbow February 1, 1908; more toxins for four months; no further recurrence of sarcoma. Carcinoma of stomach developed, causing death on May 26, 1923. (2, 54a, 81.) 17

24. (Lutman): J. S. K., male, aged 17; six times recurrent sarcoma of nasopharynx. Onset in 1906; 6 operations; removal difficult each time; rapid recurrence after each operation. Toxins (Tracy XI) given for three months in treatment of sixth recurrence; some injections were directly into the growth or periphery; tumor then removed surgically with little difficulty (had become necrotic during toxin therapy); no further recurrences. Patient married and had 6 children; in excellent health; prostatectomy July 27, 1947, for benign prostatic hypertrophy; alive and well in 1958. (29, 41, 81.) 52

25. (Oliver): Female adult; twice recurrent spindle-cell sarcoma of left axilla with supraclavicular metastases. Exact date of onset not stated. Three operations, February 1907, January 1909 and April 1909. Toxins (Tracy XI) given after third operation for three months. Metastatic masses that had reappeared after third operation and were present when toxins were begun, disappeared four weeks after toxins were stopped; no further evidence of sarcoma. Tuberculous nodules developed along the trapezius; they were removed, along with "cheesy" tonsils; no further recurrence of sarcoma when case was reported in October 1911. (84a.) 5

26. (Barnes): B. M., female, aged 12; recurrent small spindle-cell sarcoma of muscle and fibrous tissue over upper end of humerus. Onset in September 1908; excision January 30, 1909; recurrence; second excision February 6, 1910. Toxins (Tracy XI) begun six weeks later; patient contracted typhoid fever; second recurrence of sarcoma; less rapid growth; excised November 17, 1910. Toxins resumed; further small recurrence of less rapid growth; fifth excision July 3, 1911; toxins continued with intervals of rest through part of 1912, for about two years; no further recurrence until February 1916; excision; more toxin therapy. Patient married and had 1

Years traced after onset

child; later pulmonary tuberculosis developed, also severe pneumonia. Death in March 1919, apparently due to tuberculosis; no further evidence of sarcoma. (29, case 4, page 120; 41, 81.) 10½

27. (Coley): Mrs. H. W., aged 25; extensive recurrent fibrosarcoma of right arm, apparently of fascial origin, beginning to involve the periosteum of the humerus. Onset in April 1909; lesion removed surgically in November 1910; rapid recurrence of tumor 7 inches long involving ¾ of circumference of arm; considerable limitation of motion at elbow. Toxins (Tracy XI) injected into tumor, both arms and both pectoral regions; toxin therapy continued at home by family physician; total duration about twelve months; growth regressed except for fibrous stroma. Patient alive and well in 1918. (29, 73.) 9

28. (Coley and Murray): Mrs. O. S., aged 43; recurrent spindle-cell sarcoma of the parotid. Onset in the spring of 1909; excision June 1909; x-ray therapy in July and August 1909; recurrence; supraclavicular and cervical lymphadenopathy; toxins (Tracy XI and XI F) given for eight to nine months with intervals of rest; complete recovery; no further recurrence. Patient in good health next forty-seven years, except for herniotomy and fractured femur. For several years prior to death, a small nodular mobile tumor was present in the 1909 operation scar. Died from acute auricular fibrillation, on March 22, 1956, at 90 years of age. (29, 41, 81.) 47

29. (Buteau): W. K. S., male, aged 47; recurrent large round-cell sarcoma of the popliteal region. Onset September 15, 1912; incision and drainage on October 31, 1912; amputation on January 18, 1913; recurrence in stump; debridement. Toxins (Tracy XI) given for nine months thereafter, with intervals of rest; lesion in stump broke down again early in 1918 and was incised; toxins resumed in April 1918; given for another year; no further recurrences. Patient died on May 24, 1935, from chronic myocarditis. (2, 81.) 23½

30. (Coley): R. N. G., male, aged 28; recurrent myxosarcoma (neurogenic) of leg in region of the calf. Onset early in 1916; excision; recurrence two years later; growth removed with great difficulty when 3 by 5 inches in size; extensive wound fulgurated. Toxins (Tracy XI) started on third postoperative day; given intramuscularly for nine months; marked febrile reactions and chills; no further recurrence. Patient married and had 3 children; well for the next twenty-seven years; died from carcinoma of the prostate on September 5, 1945. (2, 73, 81.) 29

31. (Coley): J. St. A., male, aged 57; thrice recurrent neurogenic sarcoma of flexor surface left forearm. Onset in fall of 1916; primary tumor excised; recurred locally in nine months; excised; again recurred in nine months; was size of walnut when removed; third recurrence; 20 x-ray treatments, January to September, 1919; exploratory operation in October 1919. Toxins (Tracy XI) begun October 18, 1919; 23 injections in thirty-four days; radium pack treatment (8,250 mch.), bare tubes inserted; slight improvement; amputation at upper third of humerus; postoperative infection; drainage for five weeks; more toxins for two months; no further recurrence. Patient died from myocarditis, chronic nephritis and influenza on February 10, 1929. (41, 73.) 13

32. (Ochsner): Male, aged 10; recurrent sarcoma of antrum. Date of onset not stated. Primary tumor removed surgically in Seattle; recurrence; prognosis practically hopeless; second operation in 1917. Toxins (Parke-Davis XIII) given postoperatively for a few months; no further recurrence. Patient in good health when last traced in 1932. (81.) 15

33. (Ochsner): E. H., male, aged 18; small round-cell sarcoma of the left breast, recurrent in upper angle of scar over pectoralis major. Onset in April 1915; primary growth removed in July 1915; recurred two years later; second operation November 23, 1917. Toxins (Parke-Davis XIII) given intramuscularly above left breast and in left arm; no further recurrence. Patient in good health in 1958. (81.) 42½

Years traced after onset

34. (Coley): E. R., male, aged 44; recurrent round-cell sarcoma of left thumb. Onset in June 1921. Amputation of proximal phalanx October 24, 1921; recurrence in posterior end of metacarpal bone. Toxins (Parke-Davis XIII) given for six months; recurrent tumor regressed completely; no further recurrence. In 1942 or 1943 carcinoma of the stomach developed; operation on August 21, 1943, in Massachusetts; died from postoperative shock. (2, 41, 81.) 22

35. (Grey Turner): M. I. N., female, aged 13; recurrent alveolar sarcoma of vastus externus muscle of right thigh. Onset about October 1, 1920; tumor was size of large orange when first widely excised. Two doses of toxins given after this operation; no effect. Rapidly growing recurrent lesion in November 1922; extensive removal of tumor measuring 5 by 8 inches, December 19, 1922. Toxins (Parke-Davis XIII) given postoperatively; 15 injections in seven weeks; excellent recovery; no further recurrence. Patient alive and well in 1959. (81.) 38½

(Study XIV, a continuation, will appear in the September issue.)

REDUCED SEDATIVE EFFECT OF A NEWLY SYNTHESIZED RESERPINE DERIVATIVE (SYROSINGOPINE): CLINICAL APPRAISAL IN PRIMARY HYPERTENSION

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Although *Rauwolfia serpentina* has been known and widely used for emotional disturbances in India for many centuries, it was only about ten years ago that Vakil (1) noted additional beneficial effects in human hypertension. Three years later, Müller, Schlittler and Bein (2) isolated the pure crystalline alkaloid, reserpine, which exhibited similar pharmacologic principles. Bein (3) in 1953 and Plummer *et al.* (4) in 1954 extended the pharmacologic attributes to include quieting and reduction of emotional responses, lowering of blood pressure with bradycardia, miosis, relaxation of the nictitating membrane and hypothermia—all being consistent with reduced predominance of the sympathetic division of the autonomic nervous system.

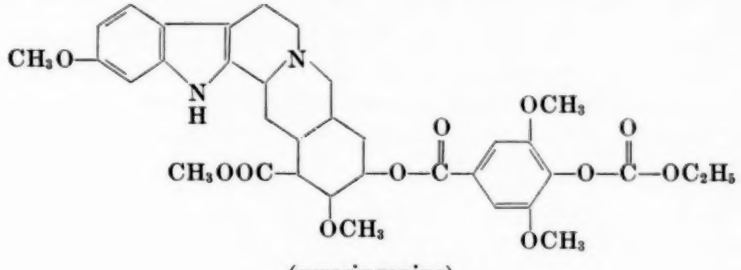
Thirty-five different alkaloids have been isolated from various Rauwolfia species but only a few of them possess enough pharmacologic activity to make their use practical. Clinically, Rauwolfia and its active alkaloids such as deserpidine and rescinnamine, have certain desirable hypotensive and sedative effects. However, in addition to their pharmacologic action on the cardiovascular and central nervous systems, these agents produce varying degrees of undesirable side-reactions such as nasal congestion, lethargy, depression, gastrointestinal upsets (diarrhea), dizziness, cold sweats, confusion, nightmares and diurnal somnolence.

It has been thought that two of the effects of reserpine — hypotension and sedation—were inseparable. However, Plummer *et al.* (5) recently noted that the sedative effect could be eliminated in dogs given a stimulant, methylphenidate (Ritalin)[1], without altering the hypotensive effect. Thus a search for possible modification of reserpine began. It was hoped that removal of the sedative factor would lessen complaints of lethargy and depression and also reduce some of the other side-effects to a minimum.

A series of chemical modifications were made by replacing different organic acids at the trimethoxybenzoic-acid portion of reserpine (6). As a result, a new substance was found which had the cardiovascular effects of reserpine, yet had minimal sedating activity. This substance (carbethoxysyringoyl methylre-

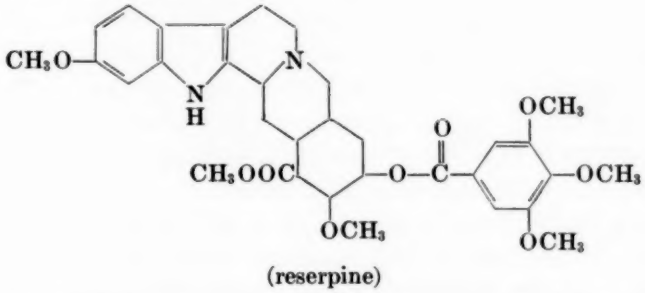
[1] Ritalin = methylphenidate hydrochloride, CIBA.

serpate or syrosingopine), originally known experimentally as Su-3118 and now known as Singoserp[2], has the following structural formula:



(syrosingopine)

Reserpine[3] is a pure alkaloid derived from the roots of *Rauwolfia serpentina* and has the following structure:



(reserpine)

Animal studies (7) showed that, with syrosingopine, not only is the sedating factor reduced but other side-effects are likewise minimized.

The hypotensive effects of reserpine and syrosingopine on the cardiovascular system were compared in both anesthetized and unanesthetized dogs. Earlier experiments had established that reserpine intravenously in a dosage of 1 mg. per Kg. produced an average drop of 40 mm. Hg in mean arterial blood pressure in a group of 12 anesthetized dogs (8). A similar drop in mean arterial blood pressure (45 ± 5 mm. Hg) was produced in 15 dogs by the same dosage of syrosingopine (Singoserp).

With either substance, the blood pressure fell gradually in a characteristic manner, reaching a minimum in three and a half to four hours. The heart rate and the response to carotid occlusion were decreased in similar degree; however, the pressor effect of epinephrine, which was heightened by reserpine, was not significantly altered by the prior administration of syrosingopine (7).

With respect to action on the central nervous system, no evidence of tranquilization in the unanesthetized normal dog was observed after 1.0 mg. per Kg. of intravenous syrosingopine (Singoserp); miosis was the only noticeable effect. Reserpine at this dosage level causes profound sedation of several days' duration. The moderate sedation caused by a single intravenous injection of

[2] Singoserp® = syrosingopine, CIBA.
[3] Serpasil®, CIBA.

0.25 mg. per Kg. of reserpine approximated that following injection of 2.5 mg. per Kg. of syrosingopine, suggesting a tenfold difference in potency between the 2 substances under the circumstances of this test. The duration of the observable effect of reserpine at the foregoing dosage level was about thirty-six hours, compared with twelve to eighteen hours following syrosingopine (7).

Chronic toxicity studies (7) carried out in dogs and rats revealed no gross or microscopic pathologic changes attributable to syrosingopine. The acute intravenous LD_{50} of syrosingopine (Singoserp) in white rats was 50 mg. per Kg., whereas that of reserpine was 18.0 mg. per Kg.

Syrosingopine has been found by Vogt (9) and Brodie (10) to release norepinephrine both centrally and peripherally, as does reserpine, although larger doses are required.

Hess (11) in 1947 observed that heightened central parasympathetic activity leads to quiescence and sleep. This suggests a possible explanation for the relationship between the central sympathetic release of norepinephrine following administration of reserpine and the sedation which is produced. Although it is also theoretical as to whether or not there is any direct relationship between central release of serotonin and reserpine-induced tranquilization, Brodie *et al.* (12) have provided evidence in favor of this view. Therefore, until we can delineate the pharmacologic and biochemical mechanisms by which reserpine modifies central nervous function, the parallelism of circulatory effects but divergence of sedative effects between syrosingopine and reserpine must await further resolution.

A nationwide survey[4] of 450 physicians using reserpine (Serpasil) in over 2,200 patients revealed that no side-effects were observed in 66 per cent of the cases. However, of those which did occur, nasal congestion was the most common (21 per cent). Other side-effects were fatigue or lethargy (10 per cent), loose stools (2.1 per cent), gastric upset (1.9 per cent), dizziness (1.2 per cent), nightmares (1.1 per cent), headache (1.0 per cent), mental depression (0.6 per cent), bradycardia (0.3 per cent) and gain in weight (0.2 per cent).

A comparison of these side-effects with those noted following administration of syrosingopine (Singoserp) in a smaller series of about 200 cases revealed a marked decrease in nasal congestion (4.7 per cent) and in fatigue or lethargy (1.9 per cent). Other complaints were comparable to those with reserpine, *i.e.*, gastric complaints (2.8 per cent), nightmares (0.9 per cent), headache (1.4 per cent) and emotional depression (0.5 per cent). No dizziness, loose stools or gains in weight have been reported thus far (13).

Since experimental evidence indicated that Singoserp had hypotensive and bradycardic effects similar to those of reserpine but with less sedation and uncomfortable nasal congestion, we decided to evaluate this new preparation as an antihypertensive drug.

CLINICAL MATERIAL AND METHODS

Forty-five white and Negro hypertensive subjects ranging in age from 37 to 62 years were carefully selected from our clinic patients. In order to establish a basis for the diag-

[4] From an I.B.M. survey questionnaire conducted by the CIBA Pharmaceutical Products Inc., Summit, New Jersey.

nosis of primary hypertension, the following data were obtained on each patient: urinalysis, electrocardiogram, chest roentgenogram, Regitine test, Funkenstein test (14), blood chemical determinations including sugar (post-prandial) and urea nitrogen, liver function tests, and an intravenous pyelogram if indicated. Patients with any hepatic, renal or metabolic disorders were eliminated from the study. All subjects were graded according to the Keith, Wagener and Barker classification (15), and were seen weekly. Blood pressure recordings were the averages of 3 determinations with the patient in the seated position. Initial and serial studies were conducted with the use of standard diagnostic equipment and conventional laboratory tests.

All previous antihypertensive medication was discontinued and placebo was used for an initial period of two to three weeks. No attempt was made to limit either the caloric or salt intake.

Singoserp was administered orally in a dosage of either 0.25 mg. or 1.0 mg. four times daily, depending on the severity of the hypertension.

RESULTS

The results in the 45 patients are listed in Table 1.

In the first group of 35 patients with hypertension classified as Grades I and II, a daily dosage of 1.0 mg. of Singoserp (0.25 mg. four times per day) was the only medication. This regimen was continued for an additional fourteen days after reduction of the arterial blood pressure, and then changed to a maintenance dosage of 0.25 mg. daily for approximately nine months. The decrease in calculated mean arterial pressure (diastolic plus $\frac{1}{3}$ pulse pressure) was statistically very significant in Grade I patients and only probably significant in Grade II.

In the second group of 10 patients with Grade III hypertension, a daily dosage of 4.0 mg. of Singoserp (1.0 mg. four times per day) was used. After a suitable period, the dosage was reduced to a maintenance level of one 1.0-mg. tablet daily for over two months. The decrease in calculated mean arterial pressure was 22 mm. Hg, which was statistically significant. The individual members of this group are listed in Table 2.

Figures 1 and 2 are examples of typical responses to syrosingopine (Singoserp). There was no gross change in body weight during the study. On the other hand, there was a reduction in pulse rate in cases in which tachycardia was present initially. The over-all incidence of side-effects was 8.8 per cent; a fourfold increase in dosage from 1 mg. to 4 mg. daily raised the incidence only from 8.6 per cent to 10 per cent.

TABLE 1

Effect of Singoserp in 45 Patients with Primary Hypertension

Grade of Hypertension	No. of Patients	Daily Dose of Singoserp (mg.)	Mean Art. B.P. (mm. Hg)		Statistical Analysis		Side-effects (No. of Cases)
			Before Rx	After Rx	t	P	
I	23	1.0	127 ± 3*	109 ± 2	5.0	<0.001	Drowsiness [2]
II	12	1.0	142 ± 5	130 ± 5	1.7	0.15	Acute urinary retention—also observed with Serpasil [1]
III	10	4.0	168 ± 7	146 ± 7	2.4	0.03	Gastric upset [1]

* Standard Error.

TABLE 2

Effect of Singoserp in 10 Patients with Grade III Hypertension

Patient			Control Blood Pressure (mm. Hg)		Blood Pressure (mm. Hg) during Singoserp Therapy	
Age (yrs.)	Race	Sex	Syst./diast.	Mean	Syst./diast.	Mean
52	W	F	162/112	129	142/88	106
59	W	M	240/132	168	164/128	140
47	C	M	268/142	184	228/128	161
62	W	F	242/124	163	180/116	137
37	C	F	280/160	200	210/148	169
48	C	F	232/130	164	200/126	151
51	C	M	274/156	195	250/154	186
55	W	F	190/130	150	150/122	131
42	W	F	228/128	161	180/116	137
61	W	M	264/126	172	198/122	147
			Av.	168 ± 7*		146 ± 7*

* Standard Error.

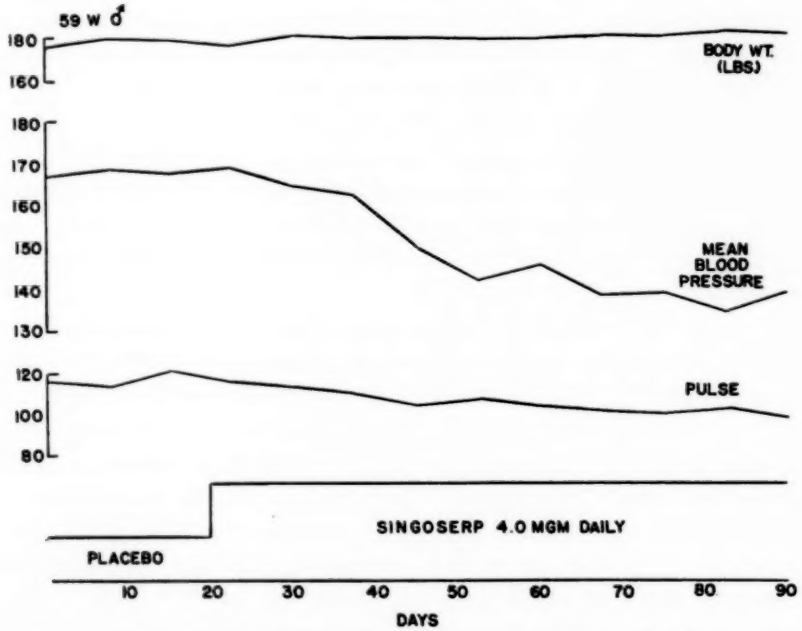


FIG. 1. Singoserp was administered orally after a control period. There was a gradual reduction of mean arterial blood pressure (mm. Hg), which reached a stable plateau in approximately thirty-three days. (Case of Grade III hypertension.)

The side-reactions so commonly observed during the use of reserpine, *i.e.*, nasal stuffiness, depression and gastro-intestinal disturbances, were not evident during treatment with syrosingopine. Of great interest was the fact that 3 of our subjects had previously complained of nasal stuffiness while taking reserpine.

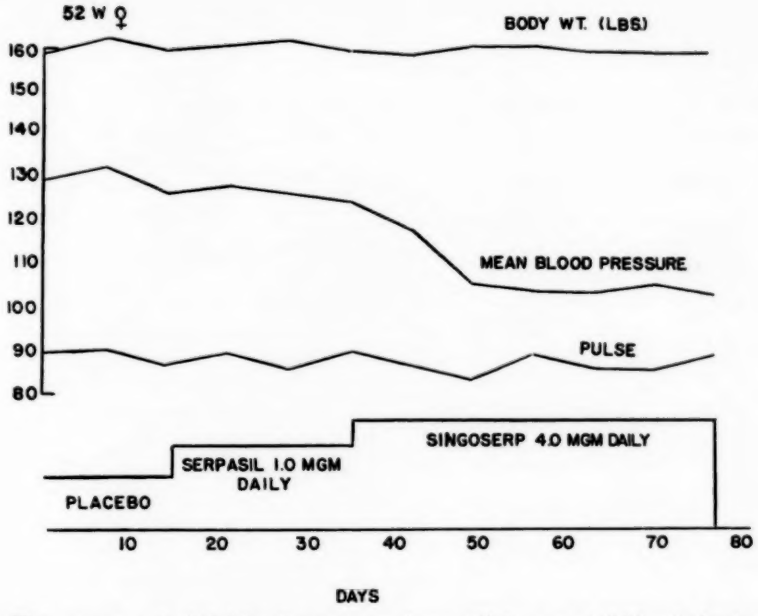


FIG. 2. The mean arterial blood pressure (mm. Hg) was stabilized during a control period followed by three weeks of Serpasil (reserpine) therapy. When Singoserp was then administered, the blood pressure was reduced and stabilized at a lower level.

TABLE 3

Antihypertensive Effect of Singoserp in White and Negro Patients

Grade of Hypertension	No. of Patients		Reduction of Mean Arterial B.P. (mm. Hg)	
	White	Negro	White	Negro
I	6	17	22 ± 3*	14 ± 2
II	4	8	16 ± 6	10 ± 4
III	6	4	24 ± 1	19 ± 5

* Standard Error.

The results of this clinical study indicated that syrosingopine was an effective antihypertensive agent with minimal side-effects. These findings were in fairly close agreement with the laboratory evidence.

During the course of our study, we noted that syrosingopine appeared to be more effective as a hypotensive agent in the white patients than in the Negro patients (Table 3). Whether or not this is due to a racial factor, and whether it holds true for reserpine and other Rauwolfia derivatives is not known.

In the course of plotting the blood pressure changes in many of our patients, we noticed an interesting phenomenon which may have some significance in the field of primary hypertension. When the mean changes were plotted, we found that in the less severe grades of hypertension the blood pressure showed a tendency to drop more quickly and sharply than in the other grades. In Grade III mild to moderate types the reductions were more gradual and required a

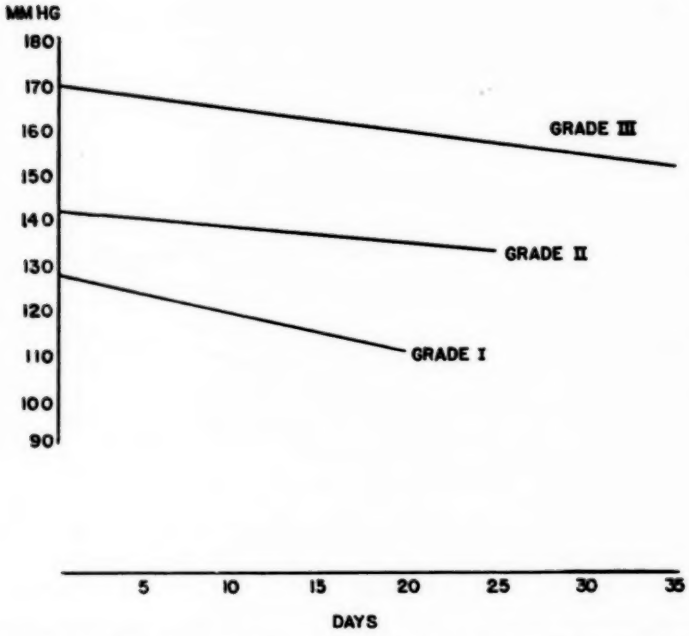


FIG. 3. Comparison of changes in mean arterial blood pressure plotted as a function of time, in 3 grades of hypertension.

slightly longer time, and in Grade III (severe) the drop was still more gradual and required a much longer time (Fig. 3).

CONCLUSIONS

Syrosingopine (Singoserp) is pharmacologically and therapeutically similar to reserpine and is a very effective hypotensive agent clinically. It may therefore be used whenever reserpine is indicated, particularly as a primary agent in Grade I hypertension and as an adjuvant in Grades II and III.

Syrosingopine is less potent dosagewise than reserpine, but equivalent therapeutic dosages are not associated with the side-effects so often observed with reserpine, particularly nasal congestion and lethargy. Since there is a broad range between effective dose and toxic dose, syrosingopine provides the practitioner with greater flexibility of dosage in antihypertensive therapy. Apparently syrosingopine is more effective in white patients with primary hypertension than in Negroes. Although this clinical evaluation is of a preliminary nature, the results indicate that this new compound is a valuable contribution to the medical management of primary hypertension.

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MEPROBAMATE-BENACTYZINE (DEPROL) IN THE TREATMENT OF CHRONIC BRAIN SYNDROME, SCHIZOPHRENIA AND SENILITY

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In chronic brain syndrome with cerebral arteriosclerosis and in senility, the psychotic manifestations run the gamut from depression to delusions characteristic of schizophrenia. The alleviation of these symptoms by phrenotropic agents, though similar, is often less successful because of organic changes in the brain. Much can be done, however, to provide months and even years of pleasant living for these patients.

Extensive trials with meprobamate in controlled and double-blind studies in over 1,000 cases have furnished a background of experience (1–7) for the present study of meprobamate combined with benactyzine hydrochloride (Deprol[1]).

The relaxing qualities of meprobamate, affecting the psyche and soma, are beneficial in the treatment of neuroses and psychoses. Meprobamate has few side-effects, none of which endanger the patient's life, and is notable for its low toxicity. Even a dose of 66 tablets (400 mg. each), taken with suicidal intent, has not been fatal. The selective action of meprobamate (Miltown, Equanil) on the thalamus and its lack of effect on the autonomic nervous system (8) make it an ideal ataraxic. Striking changes in behavior, from fear, hostility and aggression to calmness and friendliness can be produced in monkeys by meprobamate (9). A similar effect can be produced in man, with relief of anxiety, irritability, restlessness and muscular tensions (5).

Two preliminary studies of benactyzine hydrochloride alone contributed to a knowledge of its action in the neuroses and psychoses and provided background information and preparation for the study of Deprol. The first study of benactyzine hydrochloride in 60 chronic schizophrenic patients was begun in July 1956. There was some improvement in 49 per cent of the patients taking 6 to 30 mg. of benactyzine hydrochloride daily in fractional doses. A second study included patients with chronic schizophrenia, chosen in part because of a depressive factor or an element of retardation in their psychosis. The daily dosage ranged from 3 to 45 mg., and the patients were observed from one to twenty-three months. Of this group, 2 per cent were greatly improved, 24 per cent were considerably improved, and 35 per cent were slightly improved; no change was noted in 38 per cent. Side-reactions occurred in 5 per cent, and consisted of dizziness and a sense of depersonalization; these symptoms were alleviated by reduction of dosage or stopping the medication. Benactyzine hydrochloride seemed to raise the threshold for external emotional influences in many cases.

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[1] Deprol® was furnished through the courtesy of Wallace Laboratories, New Brunswick, N. J. Each tablet contains 400 mg. of meprobamate and 1 mg. of benactyzine hydrochloride.

Jacobsen and his colleagues (10) found that alterations in autonomic mechanisms due to verbal stimulus were more pronounced in normal subjects than in psychoneurotics. Moreover, there was a tendency toward inactivation by repetition of the stimulus in normal subjects, but a tendency toward exaggeration by repetition in psychoneurotics. Munro (11) found that the level of intellectual function as measured by association, abstraction and similar tests was not altered by benactyzine hydrochloride; thus it can be used in workers requiring full intellectual control. Jacobsen (12) showed that disturbed emotions can be allayed by benactyzine hydrochloride. He also demonstrated that acting peripherally it is a mild anticholinergic, and acting centrally it can normalize the behavior of rats and cats during psychic stress. That it can also exert these effects in human subjects was shown by the present study.

CLINICAL MATERIAL AND METHODS

One hundred and thirty-five cases of chronic psychosis with depression, senility, arteriosclerosis and schizophrenia were studied for periods varying from one week to seventeen months. These patients were observed daily and evaluated with regard to mental state and social behavior, both by the author and by the ward attendants. The amount of Deprol given daily ranged from 4 to 16 tablets, in fractional doses. The initial dosage was usually 1 tablet 4 times daily.

RESULTS

The results are summarized in Table 1.

During Deprol therapy, 12 per cent of the 135 patients were greatly improved, 30 per cent were considerably improved, 39 per cent were slightly improved, and 19 per cent were unchanged; thus 80 per cent showed some improvement, and 42 per cent showed considerable or great improvement. Improvement consisted of greater interest in personal affairs, a better application to work and recreation, lessening of fear and apprehension, decreased stress due to outside influences, and marked reduction in irritability and assaultiveness. Retardation or blocking in catatonic schizophrenia (sometimes mistakenly called depression) was reduced, and sleep was restored. Senility and arteriosclerosis with a depressive element were frequently benefited by Deprol, as were the depressive reactions in other types of chronic brain syndrome, and in involutional psychoses.

In general, the beneficial results became apparent within two weeks after starting therapy, though some patients showed improvement within a week and others only after a month.

Psychotic patients require much larger doses of phrenotropic drugs than do neurotic patients. Jensen (13) found that benactyzine hydrochloride in a dosage of 0.5 to 1.0 mg. three times daily was sufficient for improvement in cases of psychoneurosis, but in 4 cases of chronic psychosis a dosage of 45 mg. daily produced no side-effects. Administration of 24 tablets (400 mg. each) of meprobamate daily to patients with chronic psychosis has resulted in considerable improvement without production of side-effects. We found a similar situation with regard to Deprol therapy.

TABLE 1

Summarized Results in 135 Depressed Chronically Psychotic Patients Treated with Deprol

Dosage: 4 to 16 tablets per day (average 2 tablets 4 times daily)
Duration of treatment: 1 week to 17 months (average 1.8 months)

Results:	Greatly improved	12%
	Considerably improved	30%
	Slightly improved	39%
	Not improved	19%
		100%

(Some improvement in 80%, considerable or great improvement 42%)

Side-effects:	Drowsiness	2.9%
	Syncope	2.2%
	Dizziness	0.7%
	Restlessness	0.7%
	Dystonia	0.7%

(Side-effects in 7.2%)

		No. of patients	Avge. age (yrs.)
Diagnosis:	Schizophrenia	114	38
	Senility	8	69
	Arteriosclerosis	9	64
	Involutional psychosis	4	58
	Total	135	

Seven per cent of the patients experienced mild side-effects, including syncope, restlessness, drowsiness, dizziness and dystonia.

The need for shock therapy was entirely obviated in patients receiving Deprol either alone or in combination with chlorpromazine, perphenazine, triflupromazine, reserpine or thiopropazate dihydrochloride.

Our findings are in general agreement with those of Alexander (14), who found Deprol to be a valuable adjunct in the treatment of depression.

SUMMARY

Previous studies with meprobamate and with benactyzine hydrochloride have shown the value of these drugs in the treatment of chronic psychoses.

The effect of Deprol (a combination consisting of 400 mg. of meprobamate and 1 mg. of benactyzine hydrochloride per tablet) was studied in 135 patients with chronic psychoses and symptoms of depression. The dosage ranged from 4 to 16 tablets per day (average, 2 tablets four times daily) and the length of treatment ranged from one week to seventeen months (average, 1.8 months).

Eighty per cent of the patients were improved—42 per cent of them to a considerable or marked degree. Seven per cent experienced mild side-effects such as drowsiness, syncope, dizziness, restlessness or dystonia.

Improvement usually became apparent within two weeks, and consisted of greater interest in personal affairs, better application to work and recreation, lessening of apprehension, decreased reactions to outside stresses, and reduction in irritability and assaultiveness. The need for shock therapy was entirely obviated.

The combination of meprobamate and benactyzine (Deprol) is a useful drug in the treatment of chronic psychoses, especially those in which there is an element of depression. It is notable for its lack of severe side-effects, and is therefore preferable to many phrenotropic agents, particularly in geriatric patients.

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PROBLEMS OF MEDICAL MANAGEMENT IN HOMES FOR THE AGED*

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With more people living longer, the likelihood of chronic disease developing in the course of aging is greater today than in the past. In 1958 the life span for women was about 70.5 years, and for men about 68 years. Chronic disease usually results in chronic invalidism. According to public health statistics, there are 28 to 30 million people in the United States who are more or less disabled. Many of them are in the geriatric age group. Throughout the country there are about 25,000 nursing homes for the chronically ill and approximately 1,500 homes for the aged. The contrast between the available accommodations and the number of persons requiring such care is self-evident; the problem is to place these sick people in the proper setting.

In the past few years, since the medical and paramedical professions have become aware of the serious situation, some steps have been taken to improve the prevailing conditions in homes for the aged in order to provide better services for the chronically ill. In this paper, I shall limit my observations to homes for the aged. The modern hospital originated some centuries ago from these homes, but not until ten years ago did we realize that the bed capacity in our hospitals is not sufficient to handle all the chronically ill old people in all aspects of their needs. The result has been that homes and nursing homes have broadened their efforts to fulfill the demand and accommodate all those in the community who need their services. This situation, in turn, has created a question as to the proper function of these homes.

We call this an "Era of Transition." Homes for the aged are in a period of transition, but this era has not yet come to an end. The problem is how these homes can exist in the future without a more modern program. Along with urban and social developments, such homes will assume the role of hospitals for aged chronically ill people. It is our aim to: 1) improve the existing situation, and 2) lay the groundwork for modern geriatric hospitals throughout the country.

MODERN MEDICAL MANAGEMENT

From the standpoint of a more progressive approach to medical management, the following four "I's" should be emphasized:

1. Indoctrination of medical and allied professions and the general population.

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2. Investigation—clinical and scientific.
3. Integration of services.
4. Improvement in care.

Indoctrination

Indoctrination is one of the most difficult problems in modern geriatrics, I do not intend to sound sarcastic, but almost everyone who has dealings with geriatrics feels that he is fully aware of the problem. The fact remains that most experts do not comprehend the future course of geriatrics although, in a limited way, they are aware of the possibilities and the need for geriatric rehabilitation. It should be stressed to the medical and allied professions that homes for the aged are not dumping grounds for senile patients, but are institutions concerned with caring for people in their declining years and providing them with some type of activity and proper medical and nursing care, in the hope that at least some degree of rehabilitation may be achieved. It is important to have the understanding of professional nurses, practical nurses, nurses' aides and orderlies as well. Indoctrination of Board members is just as important, especially if further improvements are to be accomplished. Dr. Zeman, Medical Director of the Home for Aged and Infirm Hebrews in New York City, has recommended short presentations of medical issues at Board meetings. However, the major indoctrination problem concerns the relatives of the residents in the home. Typically, these relatives do not understand the situation, often because of their own feelings of guilt. The underlying factors in the misunderstanding must be cleared up, before success is attained. The general public can be approached by means of such appeals as the display of hobbies by elderly people. We should aim at: 1) a better understanding of aging in general and the education of younger persons toward graceful acceptance of it, and 2) a better understanding and more sympathetic approach toward the individual elderly patient.

It should be emphasized that old age homes are no longer isolated institutions in the community but are, or should be, busy and vital geriatric centers.

Investigation—clinical and scientific

Investigation is not referred to from a social standpoint (as when a patient is admitted to the home) but from a medical standpoint, involving clinical and scientific research. In a properly equipped home for the aged there is a great opportunity to conduct research. In a voluntary home, one has to dispel the belief that the residents and patients may be used as guinea pigs, but in any event there is enough material for wide-scale clinical evaluation while making routine periodic physical examinations. These findings should prove to be very valuable for epidemiologic studies, if good records are kept throughout the years, and they would improve our knowledge of the aging process. There is a definite place for clinico-pathologic and postmortem studies also. In this way, material in these homes can be utilized for scientific information. One of the pertinent phases in geriatric research is the evaluation of drugs. Day after day,

more and more drugs come to our attention, and we must find out how elderly patients react to them.

Integration of services

This is one of the most important considerations, from a medical standpoint. The following factors should be stressed:

1. Development of rotating medical services. In a general hospital, all specialists are well represented; therefore, in a home of the aged, under the co-ordinating efforts of the medical director, various medical specialists should be available. Periodic surveys should be conducted by experts, both as a preventive approach and for the provision of proper medical care.

2. Maintenance of close rapport between the co-ordinating medical officer, the medical staff and the psychiatrists. Rounds should be made weekly or more often with the psychiatrists, who are becoming more and more important in these institutions.

3. Correlation of the medical activities and findings with those of the social services. Homes for the aged are finding it necessary to have on the staff a social worker who is especially trained in geriatrics. The modern home for the aged (in contrast with the "almshouse" of former days) is a very busy place with its various activities, and there are many problems to solve besides the medical needs; the socio-economic needs are just as important. This means that the physician alone is not able to handle all the complex aspects of the situation; he needs the help of other experts. In the latter category I would put the dentists, dietitians, physiotherapists, the nursing staff, and all those who deal with the aged. One of the most important parts of this team is the administrative staff and its director.

A properly balanced medical program cannot be carried out without the complete cooperation of an able administrator. Foresight for the course of the home's affairs should emanate from the administration. Correlation of all the activities is the job of the director. The medical director must find his counterpart in the executive director in order to carry out a successful health program that is both curative and preventive. The groundwork for such a program should be favorable in all respects, for unless the Board and the general public recognize the need of a progressive program, success cannot be expected. There should be as little friction as possible, though it is sometimes most difficult to avoid some overlapping of spheres of activity. It is important to remember that those who are engaged in the difficult work of caring for the aged have at least one thing in common—they want to do a good job. Good organization can be developed only by regular staff meetings with proper representations of the various professions.

Improvement in care

The foregoing 3 factors constitute the basis for a progressive approach. Improvements can be likened to the roof of a building; we cannot have the roof without the building, and once we have the buliding, we must have the roof.

In the complete structure, which has to be functional as well as spiritual, we can prepare a "haven" for those who come to our attention. Improvements follow acceptance of the principles for: 1) better understanding of each other in the various professions (no prima donnas, but team workers), 2) better understanding of the patient, both medically and psychologically, and 3) better understanding of the problems which the patient and his relatives present to the staff. Patients should be treated individually and in all aspects, despite physical or mental conditions which offer the temptation to treat the disease only.

CONCLUSIONS

Medical management in a home for the aged requires a multi-disciplinary approach. Each member of the team is important and every problem must be taken into consideration. A job well done depends upon cooperation. Like the harmony of instruments in a symphonic orchestra, team work will result in harmonious conditions in the care of patients and residents in homes for the aged.

Abstracts of Current Literature

CORTISONICI ED INFARTO DEL MIOCARDIO (PREDNISONE IN MYOCARDIAL INFARCTION).

Bertola, A. *Minerva med.* **49:** 2865, 1958; through Ciba Literature Review **4:** 18, 1959.

Prednisone has a beneficial effect in myocardial infarction. It was used in 21 acutely ill patients who also received anticoagulants and coronary dilators and were at bed rest. Eight patients who received the same treatment for myocardial infarction, but without prednisone, served as controls. Two patients in the control group died; there were only 3 deaths among the 21 patients treated with prednisone. The steroid was continued for twenty to thirty days. The maintenance dosage was 5 to 10 mg. daily after larger quantities had been administered initially. The beneficial effect of the hormone consisted primarily of a rapid reduction in fever (some of the patients were afebrile by the second day), prompt relief or disappearance of precordial pain, and a feeling of well being. Blood pressure and pulse rate remained unchanged, as did blood coagulation. A diuretic effect was observed in all patients. The leukocyte count, blood sugar level, and sedimentation rate returned to normal values more quickly in the treated patients than in the controls. The electrocardiographic tracings developed similarly in both groups. Prednisone caused no untoward side-effects.

THE INFLUENCE OF ANTICOAGULANT THERAPY ON THE INCIDENCE OF THROMBO-EMBOLISM, HEMORRHAGE AND CARDIAC RUPTURE IN ACUTE MYOCARDIAL INFARCTION. CORRELATION OF CLINICAL AND AUTOPSY DATA IN 100 CASES.

Capeci, N. E., and Levy, R. L. *Am. J. Med.* **26:** 76 (Jan.) 1959.

Disagreement exists as to the value and hazards of anticoagulant therapy in acute myocardial infarction. Therefore, an analysis was made of the clinical records and necropsy reports of 100 patients who died with acute myocardial infarction. Fifty patients had received adequate anticoagulant therapy, whereas 50 patients had received none. A high percentage of error was found as to the diagnosis of infarction (in 8 treated patients, infarction was not confirmed at necropsy) and to the recognition clinically of the presence of thrombo-embolism. Thrombo-embolic complications were present with equal frequency in treated and untreated patients. The presence of congestive heart failure appeared to exert no influence upon the incidence. Major extracardiac hemorrhage was found at necropsy in 6 treated patients (12 per cent) and accounted for death in 3 of them. Such hemorrhage was not observed in untreated patients. Cardiac rupture occurred in 3 treated patients and in 1 untreated patient. This ratio also was found when the data were combined with those of 3 other studies. Unbiased conclusions cannot be drawn from studies of a selected sample of hospitalized patients. However, the examination of necropsy findings provides a way to determine the accuracy of clinical diagnoses. This study indicates some trends that seem to be well defined.

A SPECULATIVE REVIEW OF THE ROLE OF ENDOCRINE IMBALANCES IN THE GENESIS OF CERTAIN CANCERS AND DEGENERATIVE DISEASES.

Crile, G., Jr. *J. Nat. Cancer Inst.* **20:** 229, 1958, through Excerpta Med. (Geriatrics & Gerontol.) **1:** 180, 1958.

In the endocrine system, stimulation of target organs by trophic hormones increases the rate of growth of the target organs' cells and causes hyperplasia and the development

of adenomas and carcinomas. In tissues other than those of the endocrine system, there also is evidence to suggest that the growth of cells is dependent on specific trophic hormones. It is possible that the growth of each type of cell in the body is stimulated by a specific trophic hormone made by some other type of cell. A specific "self-identifying," chemical or "signal substance" made by each type of cell may control the output of the specific trophic hormone that stimulates the growth of that type of cell. Hyposecretion of "signal substances" and compensatory hypersecretion of trophic hormones may be a basic cause of cancer. There is evidence to suggest that genetic changes can be induced by alterations in the chemical environment of cells. Such changes induced by specific trophic hormones may be a major cause of cancer. Cancer may result from stimulation of a normal cell by an abnormally high concentration of a trophic hormone or it may be caused by an abnormally active response of a single cell and its descendants to a normal amount of trophic hormone. The secret of the abnormal growth that we call cancer may be revealed by further study of the factors that promote and control the growth of normal tissues.

TRANSFORMATION OF A LOW GRADE PAPILLARY CARCINOMA OF THE THYROID TO AN ANAPLASTIC CARCINOMA AFTER TREATMENT WITH RADIOIODINE.

Crile, G., Jr., and Wilson, D. H. *Surg., Gynec. & Obst.* **108:** 357 (March) 1959.

A case is reported in which, following a period of myxedema induced by treatment with I^{131}, a low grade papillary carcinoma that had shown no tendency to grow during a period of thirty-four years was transformed into a highly undifferentiated, rapidly growing, autonomous cancer. This is the fourteenth case of this type to be reported. Experimental and clinical evidence suggests that the increased output of thyroid-stimulating hormone induced by the treatment with I^{131} either initiated the transformation of the cancer to an undifferentiated and autonomous type or promoted the growth of dormant cancer cells. In order to avoid such changes, it is urged that patients with inoperable differentiated thyroid cancers be given a trial of treatment by feeding desiccated thyroid before I^{131} therapy or roentgen therapy is used. It is also urged that operable papillary carcinomas be removed, even if they are not growing, for it seems possible for some of them to undergo change to a more malignant type. (From authors' summary.)

PSYCHIATRIC PROBLEMS OF LATER LIFE. II. CLINICAL SYNDROMES.

Davis, D.; Weiss, J. M. A.; Gildea, E. F., and Mensh, I. N. *Am. Pract. & Digest Treat.* **10:** 61 (Jan.) 1959.

Older persons are subject not only to chronic brain syndrome associated with cerebral arteriosclerosis or senile brain disease and involutional psychotic reaction but to almost all psychiatric disorders. Diagnostic differentiation has become important because of the realization that many suffer from affective and neurotic disorders in which the prognosis is good. Diagnosis and treatment are essentially constant regardless of age, so long as therapy is individualized. In old people, there is little relation between the quantitative severity of changes in brain tissue and variations in clinical symptoms. Functional and organic psychoses must be differentiated. For example, the onset, history, affect, orientation, performance in psychometric tests, course, effect of electroshock therapy, and outcome in depression in old age contrast sharply with those in senile psychosis. A marked difference in outcome at six months is seen between affective psychoses and senile and cerebral arteriosclerotic syndromes in patients aged 60 years and over (Roth). At the end of two years, the differences between senile and cerebral arteriosclerotic groups are less than at six months; the latter patients have the better prognosis. Patients with delirious states at this time show an even chance of death or recovery. In the paraphrenic group, a tendency to remain in the hospital is seen. *Affective psychosis* includes all cases in which affective symptoms are a prominent consistent feature of a presenting illness. The clinical characteristics are recent onset of apathy, delusions, hypochondriasis, anxiety, restlessness, agitation, insomnia, anorexia, feelings of hopelessness, or depression with psychomotor

retardation. Affective disorders may follow retirement, bereavement, change in circumstances, loneliness, or isolation. Neurotic personality and neurotic traits occur more frequently in patients with onset before age 60. It appears that more severe stress is necessary to cause affective breakdown in persons who have been resistant during most of their lives. Therefore, physical examination of elderly persons and the treatment of physical abnormalities may help to avert affective disorders. *Senile psychosis* includes those instances in which aging is associated with gradual failure of memory and intellect, disorientation, blunting of emotions and impairment of judgment not accounted for by specific causes. There also may be reduction in initiative, disturbance of sleep, acute delirium, paranoid ideas, slowing of speech and confusion. The speech may then become fragmented, mental grasp may loosen, concentration become difficult, delusions become protean, sphincter control be lost, and bodily habits deteriorate. The symptoms depend in part upon the capacity of the personality to compensate for the brain damage; those elderly people with active intellectual interests are best able to withstand disorganization of personality. Such disorientation rarely begins before age 70 and affects more women than men. *Psychosis with cerebral arteriosclerosis* usually has its onset between the ages of 40 and 70 years and occurs primarily in men. The symptoms usually occur after cerebrovascular attacks. Half of the patients have hypertension with such symptoms as headache, dizziness, syncopal attacks, tinnitus, malaise and precordial discomfort. The course of the illness fluctuates. The intellect tends to decline slowly, but judgment, insight and personality patterns may be well preserved. Coronary artery disease and neurologic lesions are frequent complications. Epileptiform seizures occur in 15 to 20 per cent of cases. *Delirious states* are common in old age; in 30 to 40 per cent no cause can be found. In approximately half of the cases, there is an associated acute infection. Delirious states may occur with the exacerbation of an organic process or following an apoplectic attack in the course of general paresis. They also may occur in the course of senile dementia, manic-depressive psychosis, paranoid reaction, cardiac failure, chronic subdural hematoma, and combined system disease, or after operations. Approximately half of the cases in the older age group recover, so that an attack of delirium in old age should not be interpreted to indicate a progressive cerebral disease. Patients with *late paraphrenia* have a well organized system of paranoid delusions but a well preserved personality pattern and affective response. Most patients so affected are women over the age of 60 years. The prognosis in any older patient with a psychiatric disorder will depend on many factors, basic among which is the nature of the illness. Proper evaluation and diagnostic differentiation are prerequisite to proper utilization of procedures for treatment and rehabilitation.

PRESENT STATUS OF RADIOACTIVE GOLD THERAPY IN MANAGEMENT OF PROSTATIC CANCER.

Flocks, R. H.; Culp, D. A., and Elkins, H. B. *J. Urol.* **81:** 178 (Jan.) 1959.

Five hundred and seventeen patients with inoperable prostatic carcinoma but no evidence of distant metastases and with negative values for phosphatase were treated with radioactive gold. Destruction of the tumor within the prostate and in adjacent areas could be achieved by interstitial irradiation with Au^{198}. An activity of 1.5 millicuries per estimated gram of tissue was used. The solution contained 12 to 25 millicuries per cc. and the total volume averaged 4 to 6 cc. The route of access was retropubic, perineal, or transrectal. Areas of recurrence were treated again after two months. Since the destruction of grossly involved lymph nodes could not be accomplished by direct injection with radioactive gold and injection of the prostate did not spread the material to the lymph nodes, the practice was adopted of performing surgical dissection of grossly involved lymph nodes. Since node dissection was discontinuous, the colloidal gold solution was used for therapy to lymph passageways. For this purpose the material was made up in 10-cc. volume with a concentration of 3 millicuries per cc. Because of difficulties in the distribution of radioactive gold within prostatic tissue, it proved advantageous to remove large tumor masses

surgically. The total dosage of Au^{198} could thus be small, but large in comparison with the size of the remaining tumor. The mortality and morbidity associated with this type of treatment have been very low. The incidence of complications was higher in the first 50 patients, but in the remainder varied from 0.5 to 3.1 per cent for rectal ulceration, leukopenia, calculus formation and stricture of the prostatic urethra. The results of a five-year follow-up in the first 135 patients showed 42 per cent survival as compared with 30 per cent in a similar group treated by palliative means including endocrine control. Irradiation with Au^{198} is a useful addition to the armamentarium for the treatment of cancer of the prostate.

LA TERAPIA CON ANTICOAGULANTI NELLA VECCHIAIA (TREATMENT WITH ANTICOAGULANTS IN OLD AGE).

Greppi, E. *Gior. Gerontol.* **5:** 1115, 1957; through Excerpta Med. (Geriatrics & Gerontol.) **1:** 184, 1958.

The opinion that anticoagulant therapy exposes elderly patients to undesirable consequences should be corrected. Two general aspects of geriatrics should be pointed out: 1) one must distinguish between different periods of aging; 2) different constitutions must be recognized in elderly patients as well as in young ones. Therefore, hypersthenic, sturdy florid "biotypes" 50 years of age are compared with similar "biotypes" 70 years of age. For both groups, thrombophilic tendency and tolerance, and the effects of anticoagulants were examined. Considering groups of patients in whom a severe thrombophilic tendency requires stronger anticoagulant therapy, it is shown that this can be carried out in 70-year-old people as well as in those 50 years old and younger. This is based upon research carried out with such anticoagulants as Tromexan and Marcumar. The incidence and severity of hemorrhage and of intolerance, which were slight, were similar in both groups with the possible exception of slower absorption in the older. This is true in the group of hypersthenic florid, sturdy persons in whom the thrombophilic tendency is evident and predisposes to thrombotic diseases. For the other senile biotypes (with digestive and hepatic disturbances or anemia) the usual caution in the use of anticoagulant sstill is valid because different humoral and vascular alterations are present.

WHIPPLE'S DISEASE. REPORT OF FOUR CASES, INCLUDING TWO IN BROTHERS, WITH OBSERVATIONS ON PATHOLOGIC PHYSIOLOGY, DIAGNOSIS, AND TREATMENT.

Gross, J. B.: Wollaeger, E. E.; Sauer, W. G.; Huizenga, K. A.; Dahlin, D. C., and Power, M. H. *Gastroenterology* **36:** 65 (Jan.) 1959.

Whipple's disease should be suspected in middle-aged white men with a chronic, wasting, steatorrheal diarrhea associated with antecedent migratory polyarthralgia. To date, the disease appears to have affected the white race exclusively, almost always men, and usually those of middle age. Many patients have exhibited chronic cough, hives, chills and fever, ill defined abdominal distress, and marked loss of weight. On examination the patients usually appear weak and wasted; hyperpigmentation and hypotension have been found in most cases, and peripheral lymphadenopathy is a common finding. Many patients have exhibited an abdominal mass. The characteristic hematologic findings are hypochromic anemia, elevation of the sedimentation rate, and absence of macrocytosis. The concentration of serum mucoprotein is increased. Roentgenologically there is usually a deficiency pattern of the small intestine, and occasionally roentgenograms of the joints and spinal column have revealed changes suggestive of rheumatoid arthritis. Histologic examination of the peripheral lymph nodes has frequently revealed the presence of noncaseating granulomas suggestive of sarcoidosis. These nests of macrophages take the periodic acid-Schiff stain. Although this histologic picture is not by itself specific, when it occurs in a patient presenting the characteristic clinical picture, the combination should serve to make one suspect more strongly the presence of Whipple's disease. The absolute diagnosis is based

upon histologic demonstration of macrophagocytosis of the tunica propria of the small intestine and mesenteric lymph nodes, and lipogranulomatosis of the mesenteric nodes. Sprue, Addison's disease, Hodgkin's disease or other lymphoma, sarcoidosis, intra-abdominal malignancy, tuberculosis, regional enteritis, and chronic ulcerative colitis, as well as external pancreatic insufficiency must be considered in the differential diagnosis. In the 4 additional cases of Whipple's disease reported, the typical clinical and pathologic features were present. Two of the cases constitute the second recorded occurrence of Whipple's disease in siblings. The phenomenon of delayed excretion of water with regular nocturnal diuresis was demonstrable in all 3 of the cases in which this phenomenon was tested. One of these patients had a normal rate of absorption of heavy water in the fasting state. Steroid therapy of Whipple's disease has been disappointing, the benefits reported having been variable and mainly symptomatic. Spontaneous remission may occur in Whipple's disease. In 1 of the 4 patients reported there was apparently a spontaneous remission with complete disappearance of steatorrhea, lasting almost four years prior to death. (Excerpt of author's summary.)

BENIGN THYMOMA AND SELECTIVE ERYTHROID APLASIA OF THE BONE MARROW.

Jacobs, E. M.; Hutter, R. V. P.; Pool, J. L., and Ley, A. B. *Cancer* **12:** 47 (Jan.–Feb.) 1959.

Since 1922, 46 cases of selective erythroid aplasia have been reported in the literature. Twenty-six of these patients, including the 2 reported here, or 52 per cent, have had an associated benign thymoma. Among 14 patients with a benign thymoma seen since 1926, the incidence of anerythroid anemia and of myasthenia gravis was the same. Neither was found among patients with malignant thymoma. Therefore, continued hematologic study is indicated in any patient with a benign thymoma. Likewise, a search for a benign thymoma is indicated in any patient with anerythroid anemia. Thymectomy is the only effective procedure at present but it only occasionally induces a hematologic remission. Among 16 patients with this combined syndrome, only 4 (including one of the patients reported) have had a complete hematologic remission. Three others showed some improvement in the anemia. No histologic criteria could be found that would characterize thymoma with anerythroid anemia nor indicate a unique secretory activity. An attempt to demonstrate a humoral factor that would depress erythropoiesis proved unsuccessful.

HORMONAL MANAGEMENT OF THE BENIGN OBSTRUCTING PROSTATE: USE OF COMBINED ANDROGEN-ESTROGEN THERAPY.

Kaufman, J. J., and Goodwin, W. E. *J. Urol.* **81:** 165 (Jan.) 1959.

It is not proved, but evidence suggests that benign prostatic hypertrophy in elderly men may be caused by relative excess of estrogen and deficiency of androgen. Forty-four patients with obstructive benign prostatic hypertrophy were treated for six months with combined androgen and estrogen in a 20:1 ratio and followed for periods of six to twenty-four months in an attempt to determine the effects of hormone therapy. The preparation used contained 10 mg. of testosterone propionate with 0.5 mg. of diethylstilbestrol per cc. in sesame oil. It was administered in doses of 2.5 cc. three times weekly by intramuscular injection. The criteria for evaluating the results were: improvement in symptoms, improvement in voiding velocity, changes in residual urine, histologic appearance of the prostate, and prostatic size. Appreciable amelioration of symptoms and improved voiding velocity occurred in most patients. Several showed a reduction in residual urine. Histologic changes occurred in the prostate of approximately half the patients. The size of the prostate appeared to be reduced in approximately one-third. The changes produced were thought to be the result of improved bladder function, promotion of prostatic drainage, and resurgence of physical strength secondary to administration of androgen. Estrogen may have accounted for changes in the consistency, size, and histologic appearance of the prostate. The treatment of choice in benign obstructing conditions of the prostate is surgery for the patient with severe symptoms, significant residual urine, or impaired renal function.

However, in patients who are poor surgical risks or who are unwilling to undergo surgery, combined sex steroid therapy may furnish symptomatic benefit. Medical therapy in such patients places them in danger of urinary infection, urinary retention, and possible renal damage. They should be under the care of a urologist also, because of the slight possibility of stimulating occult prostatic carcinoma.

SUPRASTERNAL TRANSAORTIC CORONARY ARTERIOGRAPHY.

Lemmon, W. M.; Lehman, J. S., and Boyer, R. A. *Circulation* **19:** 47 (Jan.) 1959.

The coronary arteries can be opacified by direct needle puncture of the ascending portion of the thoracic aorta, using a suprasternal approach and injecting 90 per cent Hypaque in doses of 35 to 40 ml. Continuous electrocardiographic monitoring is carried out and an electromanometer used to record pressure waves. In 35 attempts, contrast medium could be injected in 31 (satisfactory puncture of the aorta could not be obtained in 3 patients; in 1 patient the main pulmonary artery was unintentionally opacified). Satisfactory needle puncture was accomplished, passing the needle only once in 20 instances; in the remainder, from 2 to 7 (1 patient) attempts were necessary. The procedure was undertaken for visualization of the coronary arterial system in 23 patients in order to determine whether the proximal portions were involved by atheromatous narrowing or occlusion; in 11 the objective was quantitation of aortic insufficiency; and in 1 the objective was to demonstrate a patent ductus arteriosus. With 14 of the 31 injections, no change occurred in the electrocardiogram. Transient electrocardiographic changes occurred in 7 instances at the time of insertion of the needle into the aorta, in 3 immediately after injection of medium, and in 9 during the period after injection. One instance of sino-atrial block occurred just after injection and persisted for ten minutes. In the postinjection period, T-wave inversion in 3 instances persisted one to five minutes. Subjective reactions included a transient sensation of heat and flushing, nausea, and vomiting. Four patients had a mild headache for half an hour. No cerebral dysfunction or damage could be detected clinically. No complications followed the accidental injection of a small amount of medium into the aortic wall. At operation, performed subsequently in 18 patients, ecchymosis of the anterior mediastinal tissues was observed in 3 instances. The results could be analyzed in 28 patients (3 were excluded because of difficulties encountered with the apparatus). The degree of opacification of the aorta was judged excellent in 20, fair in 4, and poor in 4; of the right coronary artery, excellent in 7, good in 3, fair in 4, poor in 3, and no opacification in 11; of the left coronary artery, excellent in 3, good in 7, fair in 8, poor in 5, and no opacification in 5. The results of coronary arteriography were compared with observations on the coronary arteries at the time of surgery in 13 patients. Essential agreement and good correlation were found in 8 cases, and partial agreement in 4 cases. In 1 patient with poor arteriographic visualization of both coronary arteries, the cause was probably aortic regurgitation, because the arteries appeared normal at the time of surgery.

ALTERNSVERÄNDERUNGEN DER SKELETTMUSKULATUR DES MENSCHEN (CHANGES IN THE SKELETAL MUSCLE DUE TO OLD AGE).

Lohmann, D.; Wielep, C., and Nöcker, J. *Ztschr. f. Alternsforsch.* **10:** 233, 1957; through Excerpta Med. (Geriatrics & Gerontol.) **1:** 179, 1958.

In patients of different ages the dry substance and the content of potassium, calcium, nitrogen, sulfur and phosphorus in 63 normal rectus femoris muscles were determined within six hours post mortem. There was an increase in the dry substance in old people, with a decrease in potassium and calcium. Nitrogen, phosphorus and sulfur showed only a slight decrease after the age of 60. ATP sensitiveness was 60 to 80 per cent in the first two decades, and declined to 10 to 30 per cent in the seventh decade. The authors think that these chemical and physical changes are the cause of the decrease of muscle function at higher ages.

SCLERODERMA OF THE LUNGS.

Miller, R. D.; Fowler, W. S., and Helmholz, F. H., Jr. *Proc. Staff Meet., Mayo Clin.* **34:** 66 (Feb. 4) 1959.

Pulmonary function was tested in 22 patients of average age 50 years (range 28 to 75 years) with scleroderma of 3.3 years' average duration. Eighteen patients had had pulmonary complaints for an average of two years, chief among which were dyspnea and cough. The patients were classified according to the amount of pulmonary fibrosis seen roentgenographically: Group 1 (none), 8 patients, 2 of whom had clinical emphysema; Group 2 (mild localized), 2; Group 3 (moderate, generalized), 2; Group 4 (severe, generalized), 10. Dyspnea was present in all except 3 patients in Group 1, 1 in Group 2, and 1 in Group 4. The vital capacity was reduced in all groups, being the lowest in Group 4 (4.5 per cent). The total capacity was reduced progressively as fibrosis became generalized and severe. Residual volume and functional residual capacity were normal in Groups 1 and 2, except for the patients with emphysema, but reduced in Groups 3 and 4. Maximal breathing capacity was less affected than vital capacity except in 3 patients, including the 2 with emphysema. Two of 9 patients tested in Group 4 had values less than 65 per cent of the predicted value. Maximal midexpiratory flow was usually in the lower range of normal but was below 50 per cent of predicted in the patients with emphysema and in 2 patients in Groups 1 and 4. The percentage of forced vital capacity expired in the first second was usually above the lower limit of normal and was reduced only in the patients with emphysema. The total ventilation (the patient seated and breathing oxygen) was greater than normal in 2 patients in Group 1 and in half of the patients in Groups 3 and 4. Hypoxemia occurred in 1 emphysematous patient and in 2 with severe generalized pulmonary fibrosis, but in none of the other patients. However, during or following exercise, it occurred in most of the patients with generalized fibrosis. Sclerodermatous involvement of the structures of the thoracic wall were thought to contribute to the small pulmonary volumes. The reduced rates of maximal expiratory flow in patients with generalized fibrosis were not interpreted to constitute clear evidence of obstructive features attributable to extensive peribronchiolar fibrosis.

ARTERIAL BYPASS BELOW THE KNEE.

Morris, G. C., Jr.; DeBakey, M. E.; Cooley, D. A., and Crawford, E. S. *Surg., Gynec. & Obst.* **108:** 321 (March) 1959.

Restoration of pulsatile blood flow in the lower leg is the objective of surgical treatment for segmental occlusive disease of the femoral artery. This objective has been reached in 86 per cent of 317 patients treated by the bypass graft technic. The proximal popliteal artery is usually suitable for distal bypass anastomosis. Satisfactory exposure of the proximal popliteal artery can be accomplished through a medial thigh incision in conjunction with a femoral incision. In certain instances, the proximal popliteal artery may be unsatisfactory for the distal bypass anastomosis because of arteriosclerotic occlusive disease or aneurysm. Exposure of the distal popliteal artery through a medial thigh incision is difficult, and posterior approach to the popliteal artery is awkward in conjunction with femoral or abdominal incisions. The distal popliteal artery may be easily approached through an anteromedial incision below the knee. This incision may be made with the patient supine, in combination with femoral and abdominal incisions. No transection or splitting of muscle or tendon is required and few, if any, collateral vessels are sacrificed. The only satisfactory anatomic path for the bypass tube from the common femoral artery to the infragenual portion of the popliteal artery is through Hunter's canal into the popliteal space and behind the popliteus muscle. The bypass tube can be tunneled between these points without difficulty and without an intermediate incision. Nine instances in which below-the-knee arterial bypass has been used in 8 patients are presented to illustrate the variable application and pathologic circumstances in which this operation appeared advantageous. (From authors' summary.)

DEPRESSIVE REACTIONS IN HYPERTENSIVE PATIENTS.

Quetsch, R. M.; Achor, R. W. P.; Litin, E. M., and Faucett, R. L. 31st Sci. Session, Am. Heart Assoc., San Francisco, October 1958; abstract *Circulation* **18:** 768 (Oct.) 1958, part 2.

Of 387 resident patients with arterial hypertension, 202 were treated with forms of *Rauwolfia serpentina*. In 53 (26 per cent), a depressive reaction developed which was moderately severe or severe in 21 patients (10 per cent). In contrast, the comparable control group of 185 hypertensive patients treated otherwise produced only 9 instances (5 per cent) of depression, of which 6 (3 per cent) were classed as moderately severe or severe. No evidence was found for any relation of depression to severity of hypertension, to drugs other than rauwolfia, or to lowering of the blood pressure. No correlation could be found between depression and age or sex or the presence of associated complicating disease. Depression occurred in 11 (58 per cent) of the 19 persons who had a history of depression prior to beginning treatment with rauwolfia and in 42 (23 per cent) of the 183 patients without such a history. There was marked variation in the dose of rauwolfia tolerated, but no depression was observed in patients taking less than 0.2 mg. of reserpine daily. Although 32 (60 per cent) of the depressive reactions occurred within the first six months after the initial use of rauwolfia, six episodes (11 per cent) developed after one year of treatment. Because of the frequency and severity of depressive reactions among hypertensive patients treated with rauwolfia preparations, indications for its use must be evaluated carefully, and whenever possible, use of the drug avoided

DAS FAULENZERHERZ (DIE PATHOGENETISCHE BEDEUTUNG KÖRPERLICHER UNTÄTIGKEIT). (THE "LAZY" HEART. THE PATHOGENETIC SIGNIFICANCE OF BODY INACTIVITY).

Raab, W. *Wien. klin. Wchnschr.* **70:** 709, 1958; through Ciba Literature Review **4:** 16, 1959.

"Lazy heart," like "television legs" in which the muscles are weak and there is a tendency to thrombosis, is a consequence of modern civilization. It may be that exercising of the arms and legs has become superfluous today in some countries, but even the most persistent sluggard can find himself in situations which place increased demands on his untrained heart muscle. In addition, it is to be expected that if the stress on the heart is constantly below normal, severe degenerative changes gradually will occur. The oxidative metabolism of the heart muscle is largely controlled by the interplay between the oxygen-consuming catechol amines (noradrenaline, adrenaline) and the oxygen-saving acetylcholine. A predominance of adrenergic influences of myocardial metabolism constitutes a threat to the myocardial oxygen balance, to cardiac dynamics which are based on the exploitation of energy and, finally, even to the structural integrity of the myocardium. An uninhibited and excessive influence of catechol amines leads to severe hypoxia and disseminated necrotic foci in the subendocardial layers of the myocardium where the danger is greatest. If, in addition, the coronary vessels show arteriosclerotic changes, the effect of catechol amines will be particularly disastrous unless—as happens in physical exertion —it is compensated for by a cholinergic counter-action.

TRIAMCINOLONE IN RHEUMATOID ARTHRITIS.

Robinson, C. E., and Robinson, H. S. *Canad. M. A. J.* **80:** 245 (Feb. 15) 1959.

Besides confirming the anti-inflammatory effect of triamcinolone, this study points up some undesirable side-effects. Disturbing weight loss occurred in 10 of the 14 patients and was progressive in some of them. The steroid had to be discontinued in 1 of these patients. The continued loss could not be accounted for by loss of sodium and water; it appeared that either protein loss or interference with protein formation must have occurred. A case report is given of a 45-year-old male patient with rheumatoid arthritis in whom renal function was borderline; upon administration of triamcinolone alone on two

separate occasions, the blood nonprotein nitrogen level reached a higher level than during therapy with equivalent doses of prednisone. This was thought to be due to the increased antianabolic or catabolic effect of the steroid. Dizziness was severe enough to require discontinuation of the steroid in 1 patient. Purpura occurred abruptly in 1 patient after the change from prednisone to triamcinolone and caused therapy to be discontinued. Moon facies and hirsutism became more marked. Acne appeared in 1 patient. One patient complained of anorexia and 2 of nausea and gastro-intestinal distress but no symptoms of ulcer. One patient with a history of peptic ulcer and 3 who had undergone gastrectomy for ulcer reported no gastro-intestinal disturbances. The 11 patients with rheumatoid arthritis, 2 with rheumatoid arthritis and psoriasis, and 1 with Marie-Strümpell spondylitis could be maintained with a dosage of 8 to 10 mg. of triamcinolone daily. The therapeutic ratio between prednisone and triamcinolone was 1.3:1, and that between cortisone and triamcinolone was 9.5:1. The 2 patients with rheumatoid arthritis and psoriasis improved while receiving triamcinolone. The substitution of triamcinolone for prednisone produced improvement in lesions of the skin and nails.

BUNDLE BRANCH BLOCK OF LONG DURATION WITH REMISSION.

Segall, S., and Spira, E. N. *Canad. M. A. J.* **80:** 248 (Feb. 15) 1959.

Five cases are presented in which remission of bundle-branch block occurred after permanent block had been assumed to be present. Normal conduction appeared in these patients after five, twelve, fourteen (2 patients) and twenty-eight months, respectively. One patient died of myocardial infarction but in the remainder the block recurred after varying intervals. The presence or absence of the block was not correlated with the severity of the disease or the prognosis. It is concluded that bundle-branch block cannot be assumed to be permanent. The fact that it is transient may be missed by making too few electrocardiograms. The possibility may exist that remission will occur at a future time.

VAGINAL HYSTERECTOMY IN THE GERIATRIC PATIENT.

Smith, L. R., and Pratt, J. H. *Obst. & Gynec.* **13:** 84 (Jan.) 1959.

A study of 324 patients 61 years of age or older indicates that vaginal hysterectomy is the method of choice in elderly women. The uterus can readily be removed from below and simultaneous repair of a cystocele and perineorrhaphy leave the pelvic floor well supported. The primary reason for this operation is prolapse, but it can be used for conditions such as fibroids, carcinoma in situ, and sometimes for carcinoma of the uterine fundus. Occasionally it may be the most reasonable way to control postmenopausal bleeding. The duration of anesthesia is short. The operation can be performed rapidly, usually with only slight blood loss, few transfusions, and few prolonged hospitalizations. The operation carries minimal risk and is well tolerated by geriatric patients. The morbidity in this series (temperature above 100.4°F. on any two days postoperatively) was 13 per cent. The principal postoperative complications are urinary retention, and cystitis; in this study, they occurred in 50 and 6 patients, respectively. Other complications included serious postoperative bleeding in 1.2 per cent, phlebitis in 1.9 per cent, and upper respiratory infection in a few patients. Vaginal hysterectomy is recommended whenever the condition is one that can be alleviated by a vaginal approach or when the patient's comfort or activities can be increased by the relief of a pelvic problem.

THE EFFECT OF CORTISONE AND CORTISOL ON 17-KETOSTEROID EXCRETION IN CARCINOMA OF THE PROSTATE AND OTHER NEOPLASMS.

Sokal, J. E.; Buchwald, L. W., and Elliott, J. *Cancer* **12:** 183 (Jan.-Feb.) 1959.

Patients with advanced cancer of the prostate were found to convert a larger percentage of administered cortisone or cortisol to 17-ketosteroids than did patients with other neo-

plasms, or patients without carcinoma. The 17-ketosteroid increment was reduced in 2 patients who were restudied after the institution of therapy for prostatic carcinoma. The rise in 17-ketosteroids is thought to be related to the metabolic activity of the tumor; studies to determine whether this is true are in progress. No explanation is as yet available for the occasional appearance of an abnormal 17-ketosteroid response in patients without carcinoma of the prostate. The response in patients with prostatic carcinoma does not constitute the basis for a cancer detection test, but it may be of limited value in the differential diagnosis of certain types of disseminated bone disease. For example, in an elderly patient thought to have Paget's disease, the occurrence of an "abnormal" (above 15 mg. in twenty-four hours) 17-ketosteroid increment led to surgical bone biopsy and the demonstration of disseminated carcinoma, after other diagnostic approaches had failed.

THE SIGNIFICANCE OF LIVER DYSFUNCTION IN MOUTH CANCER.

Trieger, N.; Taylor, G. W., and Weisberger, D. *Surg., Gynec. & Obst.* **108:** 230 (Feb.) 1959.

One hundred and fifty-two cases of carcinoma of the floor of the mouth, tonsillar fossa, and palate were reviewed. Sixty-eight had recorded information relative to the 5 "etiologic categories": tobacco and alcohol consumption, syphilis, oral irritants, and hepatic disease. Data are presented showing a sex incidence of 7.5 males to 1 female with oral cancer. Survival studies indicate a significant difference if the patients are presented in 2 groups—those with hepatic cirrhosis, and those without demonstrable hepatic cirrhosis. Cirrhotic patients with mouth cancer have a 19 per cent five-year survival rate, whereas 40.3 per cent of patients without cirrhosis survive at least five years. The average age at diagnosis for patients with carcinoma of the mouth *and* hepatic cirrhosis is 57 years; it is 70 years for patients without cirrhosis. The average for females with carcinoma of the mouth is 52 years. Oral irritants play an important role in mouth cancer, particularly if patients with lesions on the floor of the mouth are compared with those harboring tonsillar fossa carcinomas. The wearing of a dental prosthesis appears to protect from carcinoma of the hard palate. Ninety-seven per cent of the group studied smoked more than one pack of cigarettes per day. Seventy-five per cent of the patients drank alcohol to excess, 58.8 per cent of the total group had alcoholic cirrhosis, and an additional 9 per cent had nonalcoholic cirrhosis. Nine per cent of the total group had syphilis, and all but 1 of these patients were cirrhotic as well. Ten patients of the 68 studied presented additional multiple primary carcinomas of the upper gastro-intestinal or respiratory tracts, in addition to the oral cancer. The concept of co-carcinogenesis and multiple causation in cancer of the mouth is discussed with reference to a mucosal substrate previously altered by the development of hepatic disease. The factors of carcinogenic tars and chronic oral irritants are then superimposed on this prepared substrate to yield, with time, a carcinoma. (From authors' summary and conclusions.)

ESSENTIAL AMINO ACID REQUIREMENTS OF OLDER MEN IN RELATION TO TOTAL NITROGEN INTAKE.

Tuttle, S. G.; Swendseid, M. E.; Mulcare, D.; Griffith, W. H., and Bassett, S. H. *Metabolism* **8:** 61 (Jan.) 1959.

The effect was tested of increasing the intake of nitrogen on the essential amino-acid requirements of men in the sixth to eighth decades. The subjects were 8 healthy white males aged 59 to 75 years. The data from another study of 2 men are included as relevant. Seven men were tested with a diet containing 7 Gm. of nitrogen, and 8 men with a diet containing 15 Gm. of nitrogen; 5 of them received both. After receiving during a control period a diet containing approximately the same amount of nitrogen as the experimental ration, 7 men were fed a semi-synthetic diet containing quantities of essential l-amino acids equivalent to those found in 300 Gm. of whole egg with added glycine to make a total ni-

trogen intake of 7 Gm. The caloric intake was adjusted so that each man maintained or gained weight. Each remained in nitrogen equilibrium with this regimen. Eight men were given the same quantities of essential 1-amino acids with sufficient glycine and diammonium citrate added to make a total nitrogen intake of 15 Gm. Among these, a negative nitrogen balance developed in 7. The one subject who maintained nitrogen equilibrium was the only one who lost weight. The results suggest that the requirements of men over age 50 for one or more of the essential amino acids may increase as the total nitrogen intake increases. Thus, it is possible that amino-acid deficiencies may occur in men in the older age group, since their self-selected food intake is likely to be deficient in proteins of high biologic value.

LES OEDÈMES. NOUVELLES ÉTUDES BIOLOGIQUES, CLINIQUES ET THÉRAPEUTIQUES (EDEMA. NEW BIOLOGIC, CLINICAL, AND THERAPEUTIC STUDIES).

Vesin, P. *Sem. hôp. Paris* **34:** 1938, 1958; through Ciba Literature Review **3:** 294, 1958.

The elevated level of aldosterone in the blood occupies a key position in the pathogenesis of edema. Since this level must be reduced to normal if a biologic cure is to be obtained, corticosteroids are of paramount importance in the treatment of edema. Prednisone is the drug of choice for edema that has arisen as a result of cirrhosis of the liver or benign hepatitis. The effect of corticosteroids is uncertain and temporary in edema of neoplastic origin, since this type is due primarily to local factors. Edema caused by nutritional disorders and particularly protein deficiency—that is, resulting from prolonged diarrhea or gastrectomy—shows a striking response to prednisone. Corticosteroids frequently exert a beneficial effect on edema of renal origin as well. The use of prednisone to treat cardiac edema initially was regarded as controversial. In the course of time, however, good responses have been achieved, with the result that Vesin recommends corticosteroids for this purpose. It still is not possible to judge at the commencement of therapy whether or not prednisone will be effective.

USE OF TRIETHYLENE THIO-PHOSPHORAMIDE (THIO-TEPA) IN TREATMENT OF ADVANCED CARCINOMA OF PROSTATE.

Weyrauch, H. M., and Nesbit, J. D. *J. Urol.* **81:** 185 (Jan.) 1959.

Preliminary studies in 4 patients indicate that thio-TEPA may be useful as a cancericidal agent for intratumor injection in advanced prostatic carcinoma. Its chief indication is in cases in which other conservative methods have failed. It may prove helpful in the treatment of patients who refuse transurethral resection and orchiectomy, and in producing recession in carcinoma which involves the external urinary sphincter and the intramural portion of the ureter. Suppression of the bone marrow and pancytopenia may develop through the use of thio-TEPA. Such complications are reversible and avoidable by proper observation of the patient and regulation of the dosage. The cancericidal action of thio-TEPA was discovered following intraprostatic injection in a patient with proven prostatic carcinoma who had not received any benefit from conventional therapy. It has since been used successfully in 2 and unsuccessfully in 1 other patient with proven prostatic carcinoma too extensive for radical operation but without an elevated level of blood acid phosphatase or roentgenographic evidence of bony metastasis. Benefit was judged by improvement in symptomatology and recession of the neoplasm. The average single dose was 50 mg. repeated at intervals of four to six weeks, as indicated, up to four doses. The drug was diluted in a total of 10 to 15 ml. of fluid containing indigocarmine and hyaluronidase. The transurethral intraprostatic injection was made with a long flexible needle and sites were selected to ensure even distribution of the fluid throughout the neoplasm. This experience lends support to the belief that a multiple attack may prove advantageous in some cases of inoperable carcinoma of the prostate. In addition to individual susceptibility of certain

neoplasms to certain forms of therapy, it appears that some may be susceptible to multiple measures and that a combination of various agents may prove successful when one fails.

DRUG EFFECT ON THE FEMALE BLADDER AND ITS SPHINCTER MECHANISM.
Youssef, A. F. *Obst. & Gynec.* **13:** 61 (Jan.) 1959.

Cystometry and sphincterometry were used to study the effects of drugs that act on the autonomic nervous system, and of sex hormones, upon the female urinary bladder and its sphincter mechanism. These methods permit one to determine the nature of the abnormality present when a gynecologic patient complains of troublesome urinary symptoms but no gross organic urologic, gynecologic or neurologic disorder can be found. Group I comprised 110 normal women in the child-bearing period. Group II comprised patients with cystopathies, 48 in the child-bearing period and 28 who were postmenopausal. The drugs were: cholinergic (Doryl, Prostigmin); anticholinergic (Bellafoline, Buscopan); adrenergic (ephedrine, Ephetonin); antiadrenergic (Hydergine, dihydroergotamine); and sex hormones (Neo-Hombreol, Progynon-B). In Group I patients with a normal bladder, cholinergic drugs increased bladder tone but diminished the tone of the involuntary vesical sphincter. Adrenergic drugs had the opposite effect. Anticholinergic drugs moderately diminished bladder tone but did not alter that of the sphincter mechanism. Antiadrenergic drugs exerted no appreciable effect on the tone of the bladder or of its involuntary sphincter. Both estrogen and androgen were without effect on the tone of the sphincter. Bladder tone was elevated by estrogen but unaltered by androgen. In Group II patients with cystopathies, only those drugs likely to be effective in treating the patient's complaint were tried. In this group, the methods of investigation aided exact diagnosis. (*a*) In urethrotrigonitis in patients in the child-bearing period, anticholinergic drugs relieved symptoms in 10 of 13 patients. The symptoms returned and abnormal cystometric and sphincterometric findings recurred after therapy was discontinued. Lasting relief of symptoms with normalization of the cystometric curve followed androgen therapy for trigonal congestion with bladder hypertonia associated with hyperestrinism. In the bladder-neck syndrome, Hydergine improved bladder hypotonia; the elevated sphincter tone returned to normal, and the residual urine diminished. Anticholinergic drugs caused rapid disappearance of symptoms and normalization of the cystometric curve in patients with uninhibited neurogenic bladders. Except for continence in 1 patient given ephedrine, neither ephedrine tablets nor estrogen-androgen therapy relieved simple sphincter incontinence, nor improved sphincterometric findings. (*b*) Among postmenopausal patients with cystopathies, estrogen improved urethrotrigonitis (as shown by cystoscopy), and cystometry showed subsidence of bladder hypertonia. In 3 patients with weak involuntary sphincter tone, there was a rise in tone. When androgen therapy was used, it did not improve the bladder condition but did improve sphincter tone. In the bladder-neck syndrome, treatment with estrogen and Hydergine tablets produced dramatic improvement in symptoms, improvement in bladder hypotonia, and lowering of the abnormally high sphincter tone. Patients with simple sphincter incontinence that developed after the menopause became continent after estrogen-androgen therapy, and involuntary sphincter tone approached normal. Patients with a long history of incontinence were improved but not completely cured.

BOOKS RECEIVED

Receipt of the following books for review is hereby acknowledged. We are glad to publish complete listings of all new books received but such listing must be regarded as a sufficient return for the courtesy of the sender. Books of particular interest will be reviewed in full as time and space permit. Additional information in regard to all listed books will be gladly furnished upon request.

THE CARE OF THE GERIATRIC PATIENT. Edited by *E. V. Cowdry, Ph.D., Sc.D. (Hon.)*, Director of Wernse Cancer Research Laboratory, Washington University School of Medicine; formerly President of the Gerontological Society and of the Second International Gerontological Congress; Chairman of the Medical and Scientific Committee, American Society for the Aged. Inc. Cloth $8.00. Pp. 438. The C. V. Mosby Company, St. Louis, Missouri, 1958.

REVERSIBLE RENAL INSUFFICIENCY—DIAGNOSIS AND TREATMENT. By *Donald H. Atlas, M.D., Ph.D., F.A.C.P.*, Associate Professor of Medicine, Northwestern University School of Medicine; Attending Physician, Cook County and Mount Sinai Hospitals of Chicago; Senior Attending Physician, Columbus Hospital of Chicago, and *Peter Gaberman, M.D.*, late Associate Professor of Medicine, The Chicago Medical School; late Attending Physician, Cook County and Mount Sinai Hospitals of Chicago. Cloth. $7.00. Pp. 233. The Williams & Wilkins Co., Baltimore, Maryland, 1958.

THE BIRTH OF NORMAL BABIES. By *Lyon P. Strean, M.Sc., Ph.D. D.D.S. F.A.P.H.A.*, Consultant, Norristown State Hospital, Norristown, Pa.; Consultant, Montgomery Hospital, Norristown, Pa. Cloth. $3.95. Pp. 194. Twayne Publishers, Inc., New York, 1958.

AMINO ACIDS AND PEPTIDES WITH ANTIMETABOLIC ACTIVITY—Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.* and *Cecilia M. O'Connor. B.Sc.* Cloth. $8.75. Pp. 286. 28 illustrations. J. & A. Churchill Ltd., London, and Little, Brown and Company, Boston, Massachusetts, 1958.

PROCEEDINGS OF SEMINARS, 1957–1958—Duke University Council on Gerontology. *Ewald W. Busse, M.D., Chairman.* Edited by *Frances C. Jeffers, M.A.*, Executive Secretary. Paper. $1.00. Pp. 90. Duke University Council on Gerontology, Durham, N. C., November, 1958.

AMID MASTERS OF TWENTIETH CENTURY MEDICINE—A PANORAMA OF PERSONS AND PICTURES. By *Leonard G. Rowntree, M.D.*, Chairman, Medical Advisory Board, The American Legion; Chairman, Dean's Committee, V. A. Hospital, Coral Gables; Co-founder, University of Miami, School of Medicine. Cloth. About $11.50. Pp. 684. Charles C Thomas, Publisher, Springfield, Illinois; Blackwell Scientific Publications, Ltd., Oxford, England; and The Ryerson Press, Toronto, Canada, 1958.

DIFFUSE LESIONS OF THE STOMACH. By *Ian J. Wood, M.D., (Melbourne), F.R.C.P., F.R.A.C.P.*, Assistant Director of the Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, and Head of the Clinical Research Unit of the Royal Melbourne Hospital and the Walter and Eliza

Hall Institute, and *Leon I. Taft, M.B., B.S., B. Sc. (Melbourne)*, Pathologist to the Clinical Research Unit of the Royal Melbourne Hospital and Walter and Eliza Hall Institute, Melbourne, Victoria, Australia. Cloth. $6.00. Pp. 86. Edward Arnold (Publishers) Ltd., London, 1958. The Williams & Wilkins Co., Baltimore, Maryland, exclusive U. S. agents.

UROLOGY IN OUTLINE. By *T. L. Chapman, Ch.M., F.R.C.S. (Eng.), F.R.S.P.F. (Glas.)*, Honorary Clinical Lecturer in Urology (University of Glasgow), and Urological Surgeon, Victoria Infirmary, Glasgow; Urological Surgeon, Hairmyres Hospital, Lanarkshire; Urological Surgeon, Ballochmyle Hospital, Ayrshire. Cloth. $6.75. Pp. 176. E. & S. Livingstone Ltd., Edinburgh and London, 1959. The Williams & Wilkins Co., Baltimore, Maryland, exclusive U. S. agents.

NEOPLASTIC DISEASE AT VARIOUS SITES. VOLUME II. TUMORS OF THR BLADDER. General Editor *D. W. Smithers, M.D., F.R.C.P., F.F.R.* Edited by *David M. Wallace, O.B.E., M.S., F.R.C.S.*, Surgeon St. Peter's, St. Paul's, St. Philip's Hospitals; Associate Urologist, Royal Marsden Hospital; Senior Lecturer, Institute of Urology, University of London. Cloth. $11.50. Pp. 352. E. & S. Livingstone Ltd., Edinburgh and London, 1959. The Williams & Wilkins Co., Baltimore, Maryland, exclusive U. S. agents.

MUIR'S TEXT-BOOK OF PATHOLOGY. Seventh Edition. Revised by *D. F. Cappell, C.B.E., M.D., F.R.F.P.S., M.R.C.P., F.R.S. Ed.*, Professor of Pathology, University of Glasgow; Pathologist to the Western Hospitals Group, Glasgow; Consultant Pathologist to the Western Regional Board. Cloth. $14.50. Pp. 1201. Edward Arnold (Publishers) Ltd., London, 1958. The Williams & Wilkins Co., Baltimore, Maryland, exclusive U.S. agents.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. 24,Tagung, Bad Nauheim vom.11. bis 13. April, 1958. Thema: DIE LEBENSWANDLUNGEN DER KREISLAUFORGANE IN ABHÄNGIGKEIT VON ALTER UND GESCHLECHT. Herausgegeben von *Prof. Dr. Rudolf Thauer*. Mit 163 Abbildungen. Dr. Dietrich Steinkopff Verlag, Darmstadt, 1958.

THE PATHOLOGY AND MANAGEMENT OF PORTAL HYPERTENSION. By *R. Milnes Walker, M.S., F.R.C.S.*, Professor of Surgery, University of Bristol. Cloth $8.00. Pp. 113. Edward Arnold (Publishers) Ltd., London, 1959.

GROVES' SYNOPSIS OF SURGERY. Fifteenth Edition. Edited by *Sir Cecil Wakeley, Br., K.B.E., C.B., L.L.D., M.Ch., D.Sc., F.R.C.S., F.R.S.E., F.A.C.S. F.R.A.C.S.*, Past President of the Royal College of Surgeons of England; Fellow of King's College, London; Consulting Surgeon to King's College Hospital and Belgrave Hospital for Children; Senior Surgeon, Royal Masonic Hospital; Consulting Surgeon to the Royal Navy; Examiner in Surgery to the University of Liverpool; Formerly Examiner in Surgery to the Universities of Bristol, Cambridge, Durham, Glasgow, London, and Sheffield; and to the National Universities of Ireland and Wales. Cloth. $8.50. Pp. 650. John Wright & Sons Ltd., Bristol, 1958. The Williams & Wilkins Co., Baltimore, Maryland, exclusive U.S. agents.

THE EFFECT OF PHARMACOLOGIC AGENTS ON THE NERVOUS SYSTEM.—PRO-

CEEDINGS OF THE ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE, VOLUME XXXVII, December 13 and 14, 1957, New York. Editor: *Francis J. Braceland, M.D.* With 124 illustrations and 34 tables. Cloth. $13.50. The Williams & Wilkins Company, Baltimore, Maryland, 1959.

ON AGEING AND OLD AGE. BASIC PROBLEMS AND HISTORIC ASPECTS OF GERONTOLOGY AND GERIATRICS. By *M. D. Grmek, M.D.* (*Zagreb*). Paper. 14 Guilders. Pp. 106. Dr. W. Junk, Publishers, The Hague, Netherlands (13, van Stolkweg), 1958.

Books for review should be sent to Edward Henderson, M.D., Editor-in-Chief, 236 Midland Avenue, Montclair, New Jersey.

NEWS AND NOTICES

AMERICAN INSTITUTE OF ULTRASONICS IN MEDICINE

The Annual Meeting of The American Institute of Ultrasonics in Medicine will be held on *September 2, 1959* at the Leamington Hotel, Minneapolis, Minnesota. The guest speaker at the Luncheon Meeting will be Russell Meyers, M.D., Professor of Surgery and Chairman, Division of Neurosurgery, State University of Iowa Hospitals and College of Medicine, who will discuss "The Potentials of Ultrasonics in General Surgery and Surgical Specialties." For further information apply to John H. Aldes, M.D., Secretary, 4833 Fountain Avenue, Los Angeles 29, California.

THE ACADEMY OF PSYCHOSOMATIC MEDICINE

The Sixth Annual Meeting of The Academy of Psychosomatic Medicine will be held *October 15–17, 1959* at the Sheraton-Cleveland Hotel in Cleveland. The meeting will be oriented and directed to fit the needs of nonpsychiatric physicians. Practical everyday office management of psychosomatic problems and emotional disturbances will be dealt with in formal papers, symposia, panel discussions, and small study groups. The meeting will be open to all scientific disciplines, as well as psychologists, social workers and nurses. Information may be obtained from Dr. Bertram B. Moss, Suite 1035, 55 East Washington Street, Chicago 2, Illinois.